Adrenergics and antiadrenergics

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Introduction

- **Acetylcholine** is the crucial neurotransmitter in the cholinergic system and has specific actions at various synapses and tissues. The wider spectrum of second messengers are produced if muscarinic receptors (GPCR) are activated. Thus, various second messengers are produced which can affect cellular contraction, excretions and others.

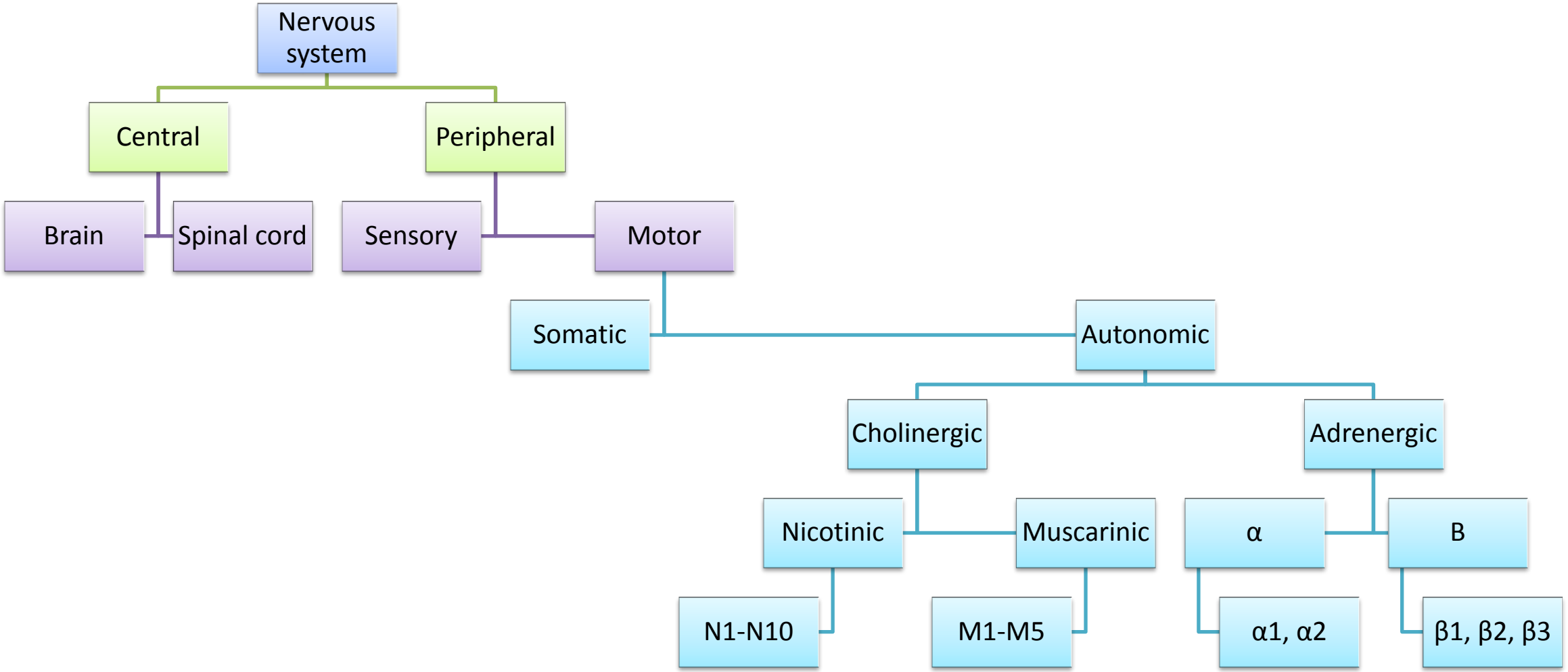
- Similarly, a**drenaline** and **noradrenaline** are crucial neurotramitters in the adrenergic system. Adrenergic receptors are also belong to GPCR, thus the spectrum of second messangers are also wide, however, the results on the cell are opposite to those of cholinergic receptors.
  - Noradrenaline is released at neuromuscular junctions, thus affects enervated tissues
  - While adrenaline is released into blood (during fight or flight) and affects enervated and unenervated tissues

The action of noradrenaline at various tissues is the opposite to that of acetylcholine, which means that tissues are under a dual control. For example, if noradrenaline has a stimulant activity at a specific tissue, acetylcholine has an inhibitory activity at that same tissue.

Both the cholinergic and adrenergic systems have a 'background' activity, so the situation is analogous to driving a car with one foot on the brake and one foot on the accelerator.

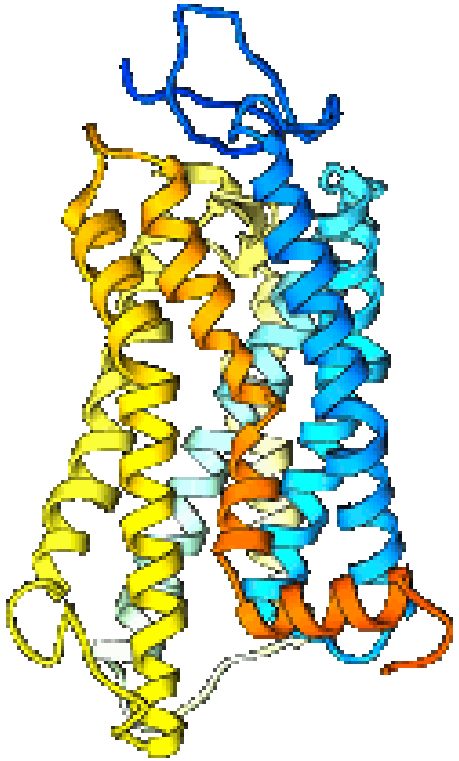
The overall effect on the tissue depends on which effect is predominant.

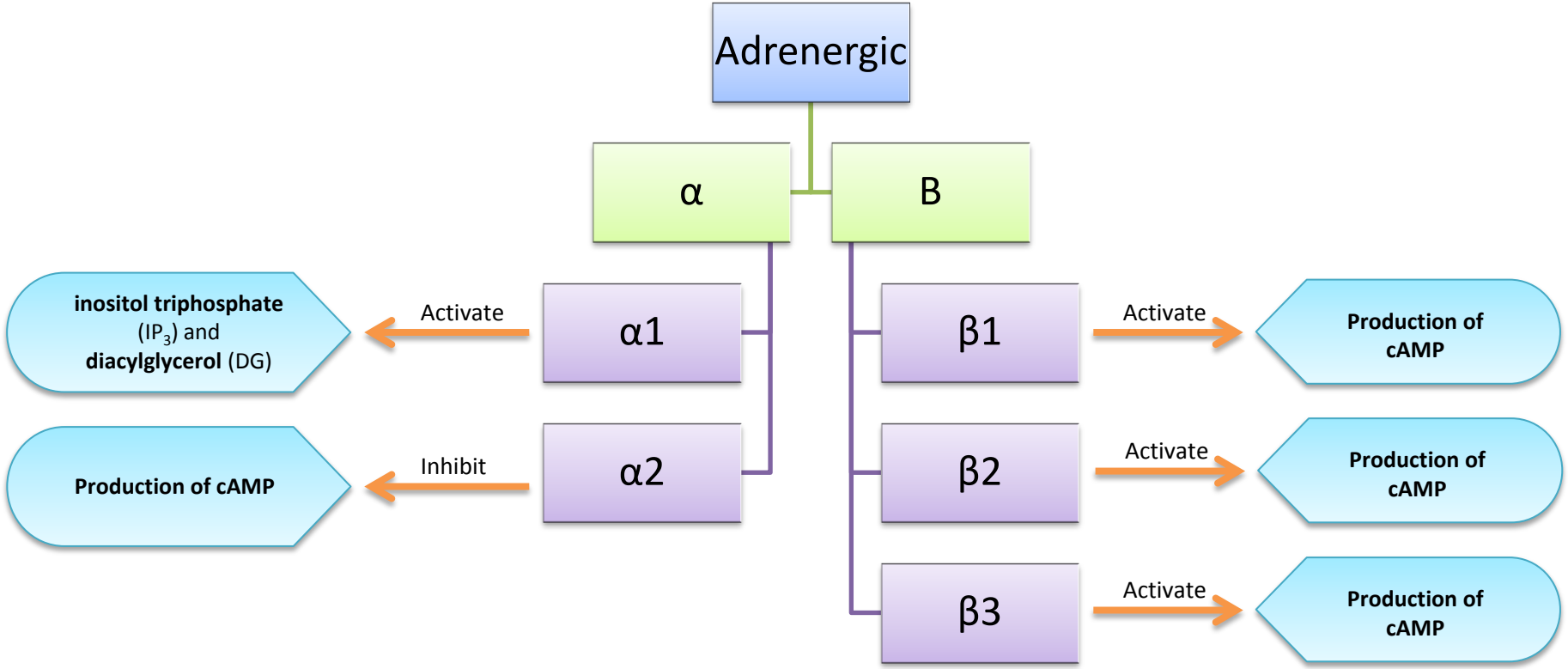
Classification of neurons



Adrenergic receptor subtypes

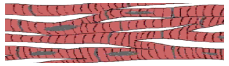
- Similar to acetylcholine receptors, adrenergic receptors are of two main types; α and β-adrenoceptors.
- Unlike acetylcholine receptors, both α and β-adrenoceptors belong to GPCR family of switches.





All of these adrenergic receptor types and subtypes are 'switched on' by adrenaline and noradrenaline, but the fact that they have slightly different structures means that it should be possible to design selective agonists that can distinguish between them.

TABLE 23.1 Distribution and effects of adrenoceptors in different parts of the body

	Organ or tissue	Predominant adrenoceptors	Effect of activation	Physiological effect
	Heart muscle	β_1	Muscle contraction	Increased heart rate and force
	Bronchial smooth muscle	α_1	Smooth muscle contraction	Closes airways
		β_2	Smooth muscle relaxation	Dilates and opens airways
	Arteriole smooth muscle (not supplying muscles)	α	Smooth muscle contraction	Constricts arterioles and increases blood pressure (hypertension)
	Arteriole smooth muscle (supplying muscle)	β_2	Smooth muscle relaxation	Dilates arterioles and increases blood supply to muscles
	Veins	α	Smooth muscle contraction	Constricts veins and increases blood pressure (hypertension)
		β_2	Smooth muscle relaxation	Dilates veins and decreases blood pressure (hypotension)
	Liver	α_1 & β_2	Activates enzymes which metabolize glycogen and deactivates enzymes which synthesize glycogen	Breakdown of glycogen to produce glucose
	Gastrointestinal tract smooth muscle	α_1, α_2, and β_2	Relaxation	'shuts down' digestion
	Kidney	β_2	Increases renin secretion	Increases blood pressure
	Fat cells	β_3	Activates enzymes	Fat breakdown

Adrenergic receptor subtypes (Cont.)

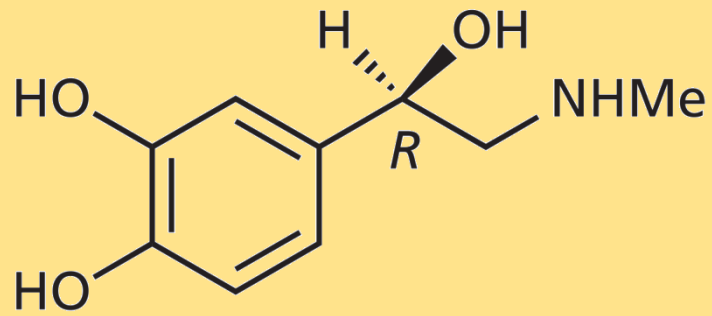
- Activation of α-receptors generally contracts smooth muscle (except in the gut),
- Whereas activation of β-receptors (mostly β2) generally relaxes smooth muscle.
- In the heart, the β1 -adrenoceptors predominate and activation results in contraction of muscle.

- **Different types of adrenoceptor explain why adrenaline can have different effects at different parts of the body.**

- In general, stimulation of the sympathetic nervous system causes what is known as a “fight-or-flight” response. These effects include:
  1. Increased rate and force of heart contraction
  2. Rise in blood pressure
  3. Shift of blood flow to skeletal muscles
  4. Dilation of bronchioles and pupils
  5. Increase in blood glucose levels through gluconeogenesis and glycogenolysis.

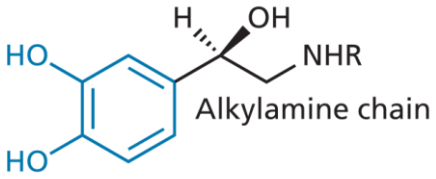
Endogenous adrenergic receptor agonists

- The endogenous compounds which can switch adrenosceptor switches to ON are belong to catecholamine group of compounds.

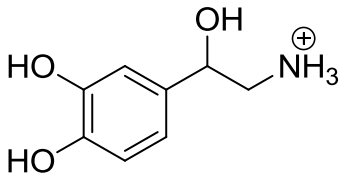


Adrenaline

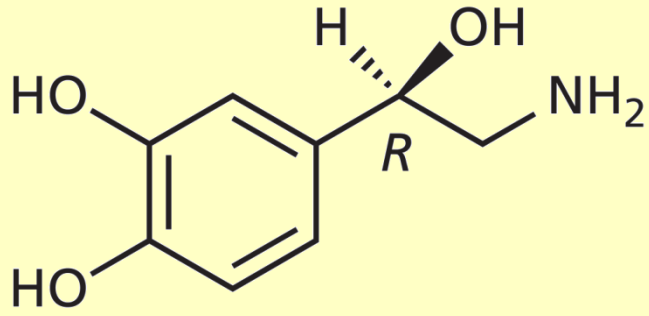
The overall effect of adrenaline is to increase blood pressure by vasoconstriction to non-skeletal muscles (which have α_1 receptors), increase blood flow to skeletal muscles (which have β_2 receptors) and increase rate of beat of heart (which have β_1 receptors)



Catechol ring system



Chemically, they are less stable and protonated in blood pH

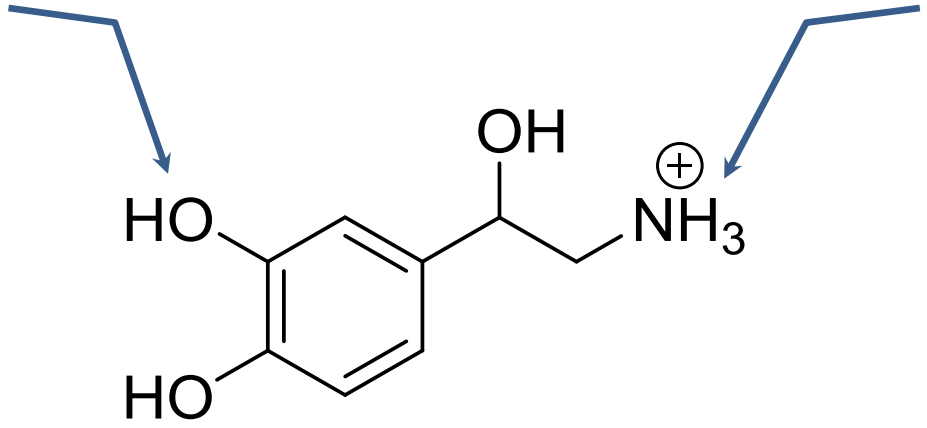


Noradrenaline

Similar to adrenaline except it has lower affinity to α_1 receptors, thus cause no vasoconstriction.

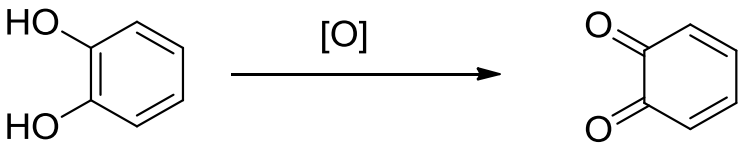
Chemistry of adrenergic agonists

- Weak acid (pKa = 8.7)
- Polar and water soluble
- Log P = -0.6
- Easily oxidized to colored quinone analogue
- Metabolized by COMT



Adrenaline

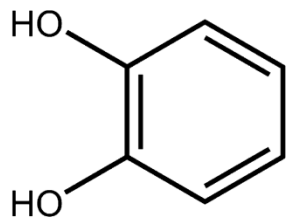
- Weak base (pKa =10)
- Protonated form is mainly present at physiological pH
- Metabolized by MAO



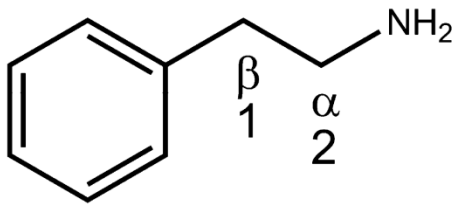
Colored quinone

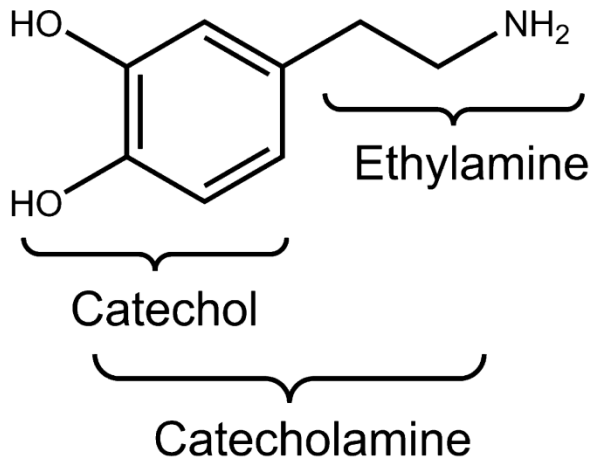
Low stability, Low oral absorption, Low penetration to CNS and short duration of action

Endogenous adrenergic receptor agonists



ortho-dihydroxybenzene moiety

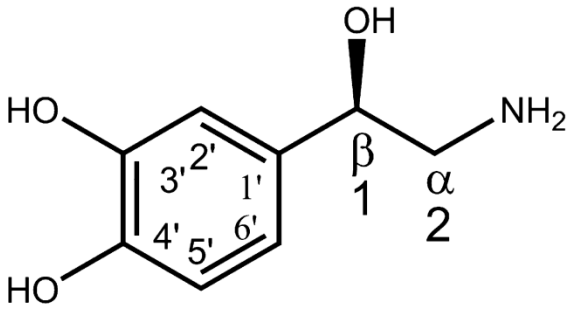


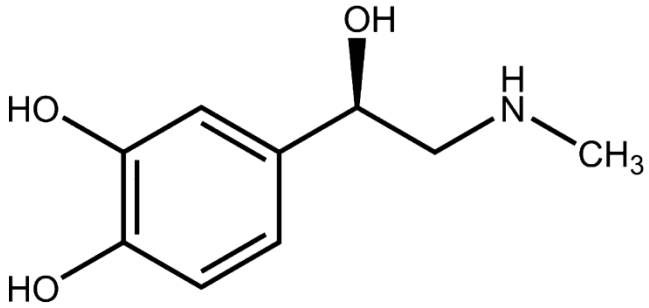


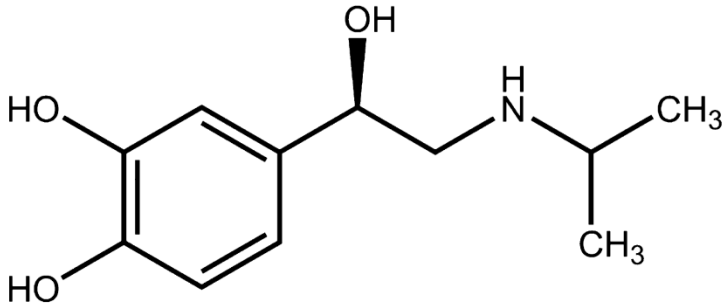
Catechol

β-Phenylethylamine

Dopamine (DA)







Norepinephrine (NE)

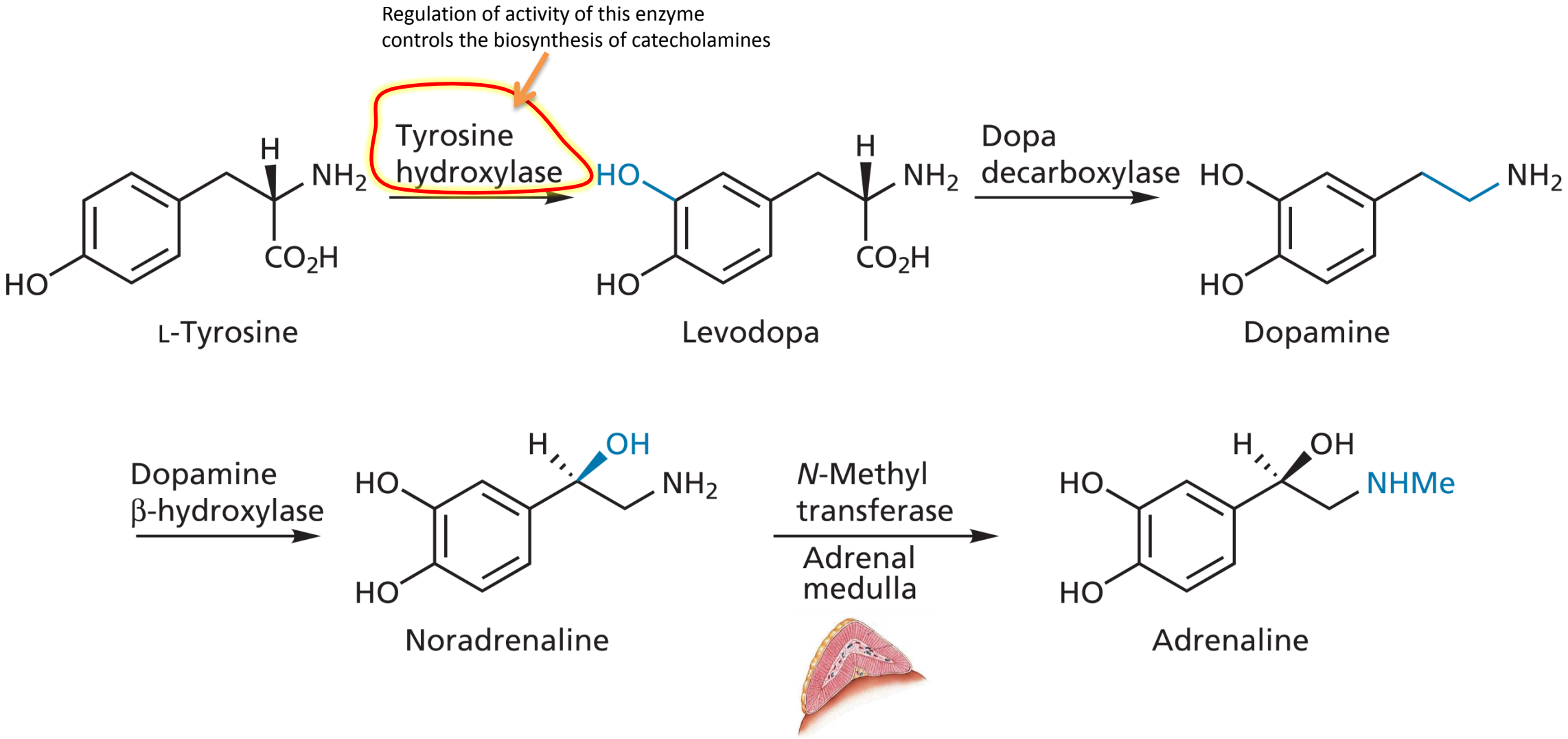
Epinephrine (E)

Isoproterenol (ISO)

Figure 16.1 ● Adrenergic neurotransmitters and related compounds.

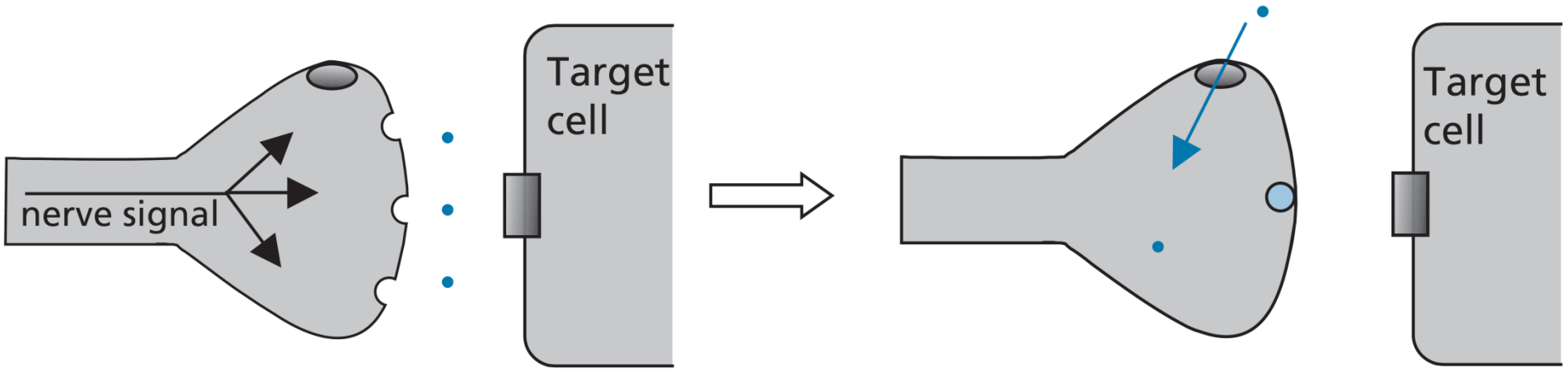
Synthesis of endogenous adrenergic receptor agonists

- The biosynthesis of noradrenaline and adrenaline starts from the amino acid **L-tyrosine**



Release of endogenous adrenergic receptor agonists

- Noradrenaline is biosynthesized in a presynaptic neuron then stored in membrane-bound vesicles.
- When a nerve impulse arrives at the terminus of a neuron noradrenaline is released into synapse.
- After activating the post-synaptic receptor, noradrenaline is taken back by the pre-synaptic receptor for metabolism or repackaging.
- Other co-neurotransmitters are released from the vesicles along with such as **Adenosine triphosphate** (**ATP**) and a protein called **chromogranin A** and they act on their own post-synaptic receptors.



Vesicles fuse and release transmitter

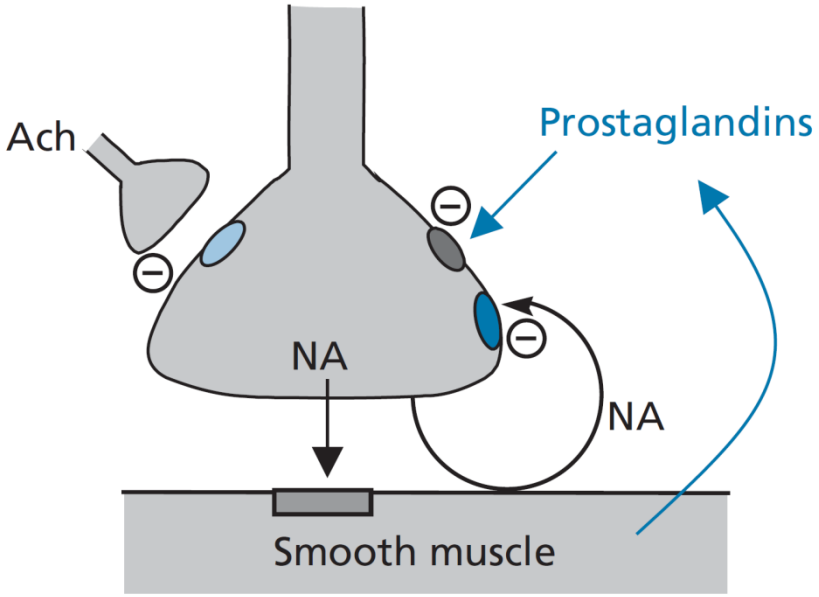
Neurotransmitter reabsorbed by active transport

Presynaptic receptors and control

- which interacts with released noradrenaline and has an inhibitory effect on further release of noradrenaline.
- Presynaptic receptors are present to control the release of adrenaline at the synapse

- **<u>Types of presynaptic receptors in adrenergic neurons:</u>**

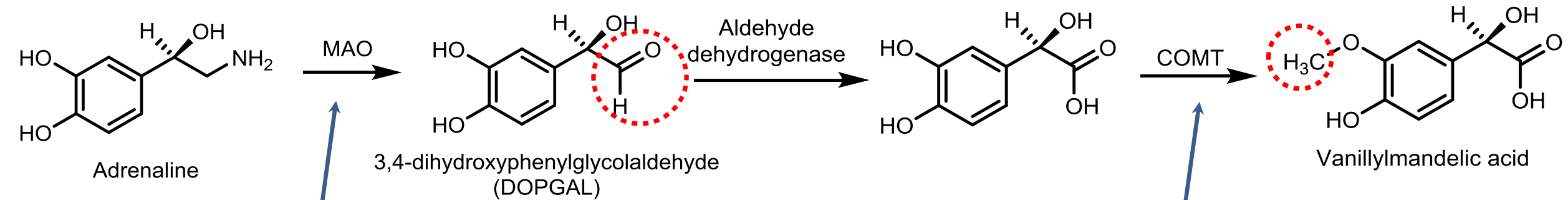
1. **α2 – adrenoceptors:** which inhibit the further release of noradrenaline
2. **Prostaglandin receptors: PGE_2** appears to inhibit transmission, whereas **$PGF_{2\alpha}$** appears to facilitate it. Because different cells release different PGs, they will have different response to adrenergic stimulation
3. **Acetylcholine receptor:** which inhibit the further release of noradrenaline, thus let the parasympathetic system affects the sympathetic system.



Metabolism of adrenergic receptor agonists

- Catecholamines are metabolized in the periphery into inactive aldehyde by two enzymes
  1. Monoamine oxidase (MAO)
  2. Catechol O –methyltransferase (COMT)

- Metabolism in the CNS is slightly different, but still involves MAO and COMT as the initial enzymes.



Controls the duration of signal
(conc of NE in synapse)

Controls the duration of action
(conc of NE in tissue)

Metabolism of adrenergic neurotransmitters

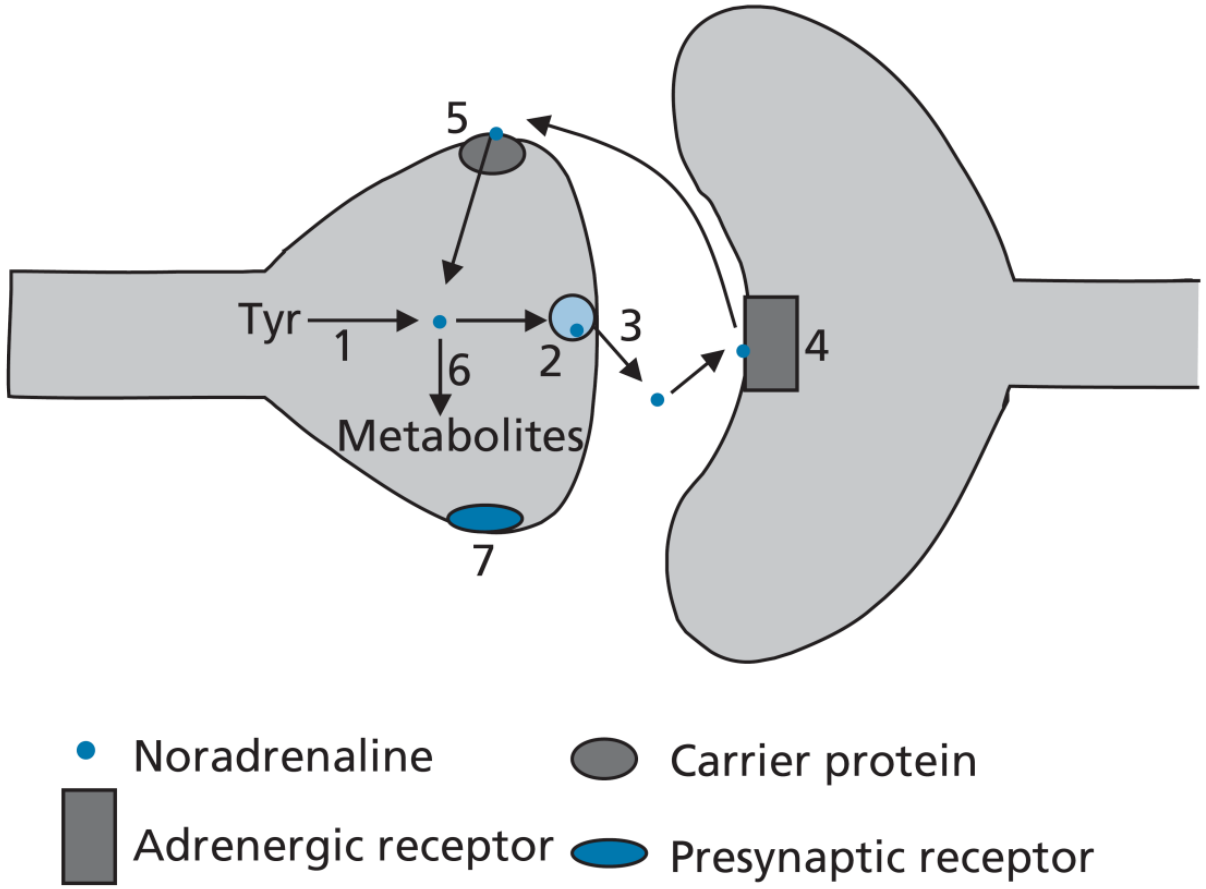
	MAO	COMT
Location	- Neuronal mitochondria - Metabolism of intraneuronal CAs	- Outside neuron - Metabolism of extraneuronal Cas
Reaction	- Deamintes CAs ➔ aldehydes	- O-methylate CAs ➔3'-Ome-Cas
Substrates	Compounds with terminal aliphatic amine (1° or 2°) - **MAO-A**: NE and 5-HT - **MAO-B**: DA, β-phenylethylamine, benzylamine	- DA, E, NE, ISO, etc.

Signal termination of adrenergic receptor agonists

- Once noradrenaline (NE) has exerted its effect at adrenergic receptors, there must be mechanisms for removing the NE from the synapse and terminating its action at the receptors. These mechanisms include:
  (a) reuptake of NE into the presynaptic neuron (recycling, major mechanism) by NET and into extraneuronal tissues (uptake-I)
  (b) conversion of NE to an inactive metabolite
  (c) diffusion of the NE away from the synapse (uptake-II).
- The first two of these mechanisms require specific transport proteins or enzymes, and therefore are targets for pharmacologic intervention
- Best substrate for NET is norepinephrine beside others. NET can be inhibited by cocaine and some of the tricyclic antidepressants

Possible drug targets to affect adrenergic system

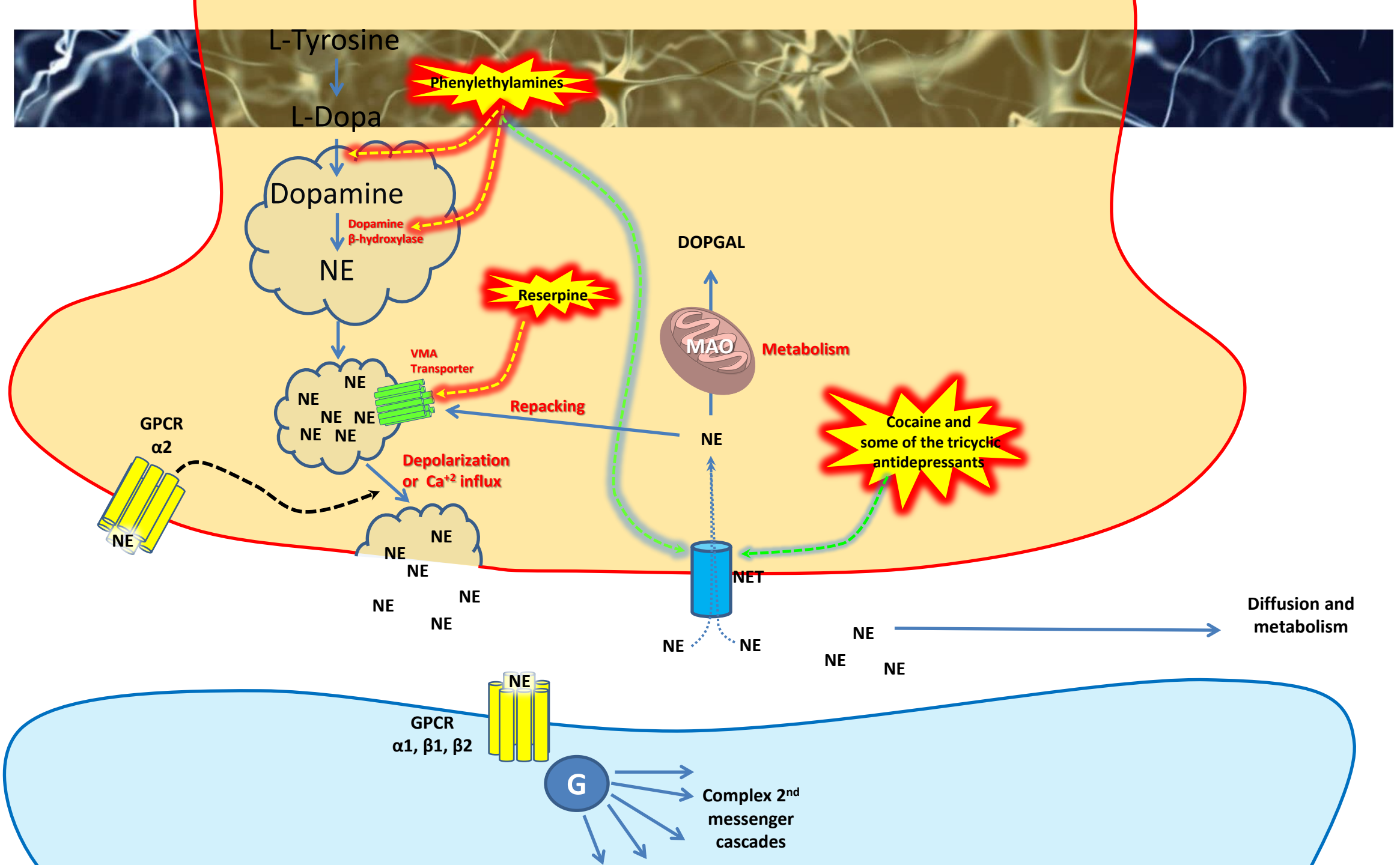
- Several potential drug targets are available to affect noradrenaline signaling:
  1. Biosynthesis of noradrenaline
  2. Packaging of noradrenaline
  3. Release of noradrenaline package
  4. Stimulation of post-synaptic receptor
  5. Re-uptaking of released noradrenaline
  6. Metabolism of uptaken noradrenaline
  7. Stimulation of presynaptic receptors.



Possible drug targets to affect adrenergic system (Cont.)

- Drug intervention targets include:

1. DOPA decarboxylase
2. Vesicular monoamine transporter (VMAT): 12-helix membrane–spanning proton antiporter. It transport NE into vesicles. In the vesicles NE is held in a stable complex with adenotriphosphate (ATP) and proteins. reserpine, block this transport, preventing the refilling of synaptic vesicles
3. dopamine β-hydroxylase is attached to vesicle: it has low specificity and can hydroxylase different phenylethylamines such as tyramine (to octopamine), α-methyldopamine)to α –methylnorepinephrine) which forms false neurotransmitters.
4. phenylethanolamine-*N*-methyltransferase (PNMT): present in adrenal medulla. It has low specificity and can transfers methyl groups from *S*-adenosyl methionine (SAM) to the nitrogen atom on various β-phenylethanolamines.
5. the entrance of Ca+2 into these cells results in the extrusion of NE by exocytosis of the granules. Indirectly acting and mixed sympathomimetics (e.g., tyramine, amphetamines, and ephedrine) are capable of releasing stored transmitter from noradrenergic nerve endings by a calcium-independent process. They are excellent substrates for NE reuptake transporter (NET) and VMAT. Thus displacing NE from vesicle without exocytosis.


L-Tyrosine
L-Dopa
Phenylethylamines
Dopamine
Dopamine β-hydroxylase
NE
Reserpine
VMA Transporter
DOPGAL
MAO
Metabolism
Repacking
Cocaine and some of the tricyclic antidepressants
GPCR α2
Depolarization or Ca+2 influx
NET
Diffusion and metabolism
GPCR α1, β1, β2
G
Complex 2nd messenger cascades

Modes of action for drug targets affecting adrenergic system

- According to drug target and final effect on adrenergic activity, the drugs can be classified into:

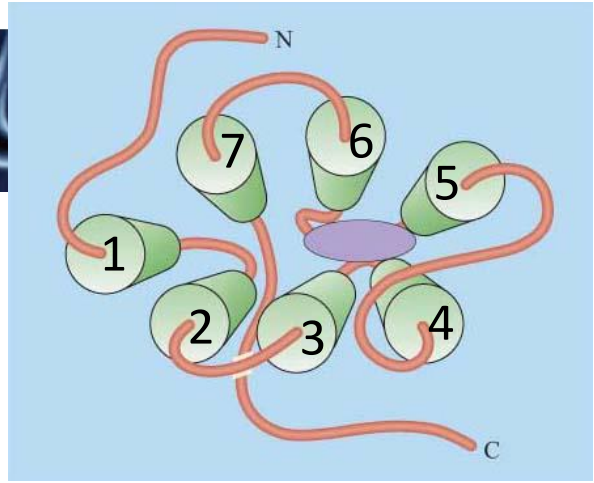
1. **Switch modulators (act on adrenergic receptor):**

- **Agonists:** stabilize switch to ON (e.g. adrenaline, salbutamol, clonidine, etc.)
- **Antagonists:** stabilize switch to OFF (e.g. antihypertensive agents)

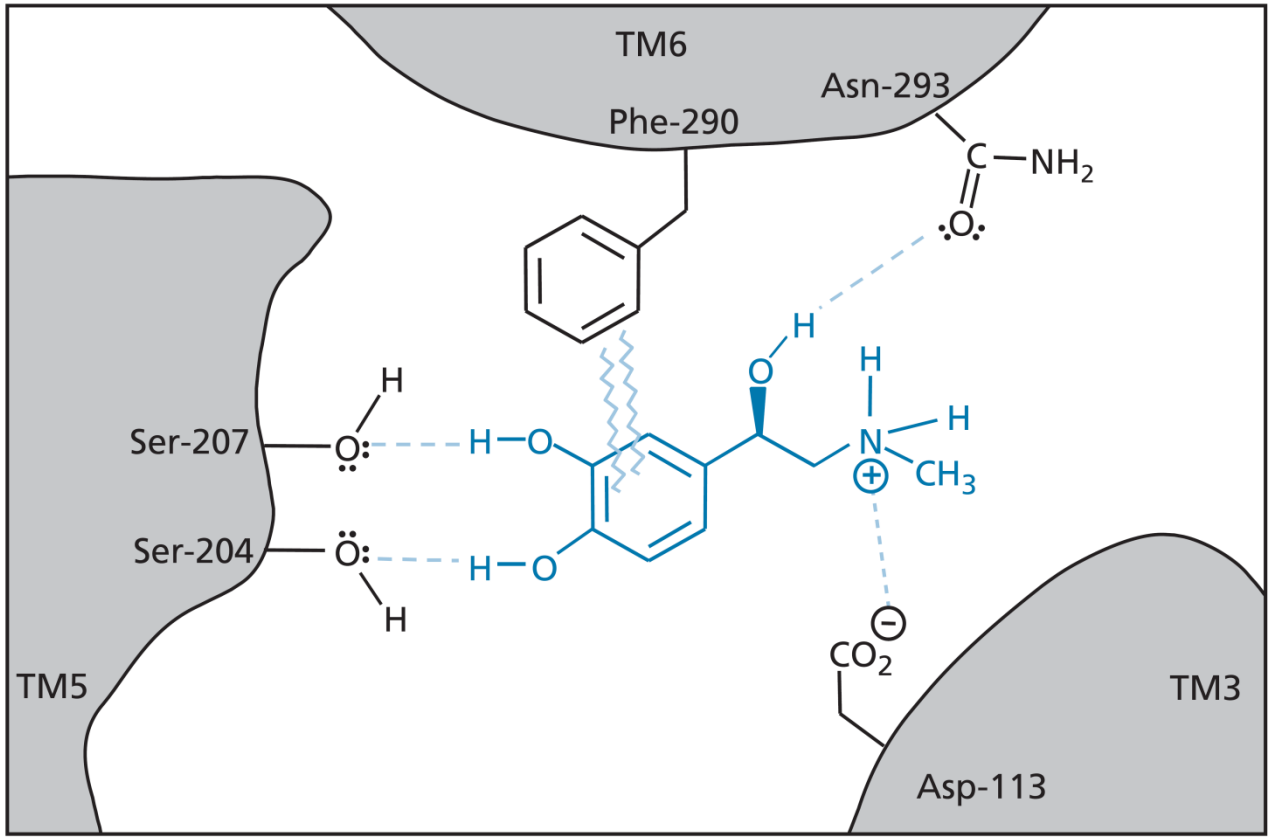
2. **Non-switch modulators (act on neurotransmitter synthesis, release, reuptake and metabolism)**

- **Agonist like:** increase the availability of neurotransmitter (amphetamine, etc.)
- **Antagonist like:** decrease the availability of neurotransmitter (metyrosine, carbidopa, reserpine, etc.)

Binding site of adrenergic receptor

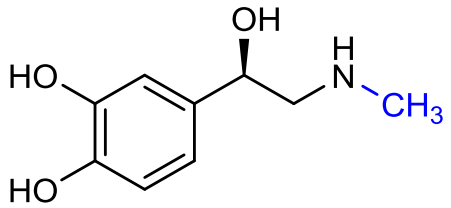


- The adrenergic receptors are G-protein-linked receptors which consist of 7 transmembrane (TM) helices
- It was proposed that mainly 3 out of the 7 TM helices (i.e. TM3, TM5, and TM6) are involved in the binding site.
- Within the binding site, aspartic acid residue (Asp-113), a phenylalanine residue (Phe-290), and two serine residues (Ser-207 and Ser-204) are involved in interactions with adrenaline or noradrenaline.
  - The serine residues interact with the phenolic groups of the catecholamine via hydrogen bonding.
  - The aromatic ring of Phe-290 interacts with the catechol ring by van der Waals interactions,
  - while Asp-113 interacts with the protonated nitrogen of the catecholamine by ionic bonding.
  - There is also a proposed hydrogen bonding interaction between Asn-293 and the alcohol function of the catecholamine.

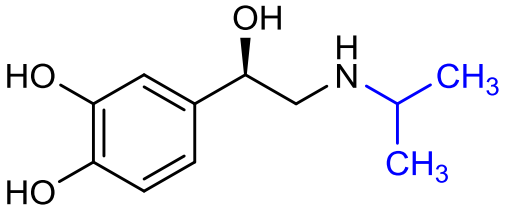


Difference between binding sites of adrenergic receptor subtypes

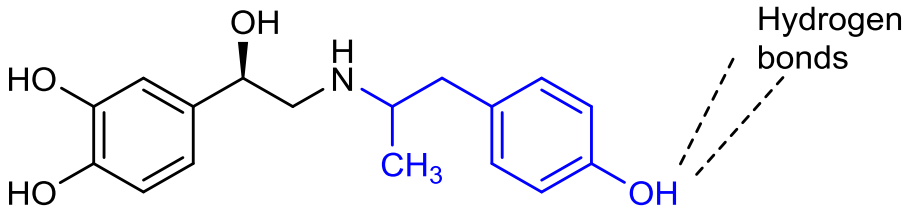
1. **The N-alkylation** determines selectivity toward α- or β-receptors.
   - Small alkyl (N-CH_3) ➔ α > β (e.g. adrenaline)
   - Large alkyl (N-isopropyl) α < β (e.g. isoprenaline)
     (N- tert-butyl) α < β
   - The affinity to receptor is increased by terminating the alkyl with polar group



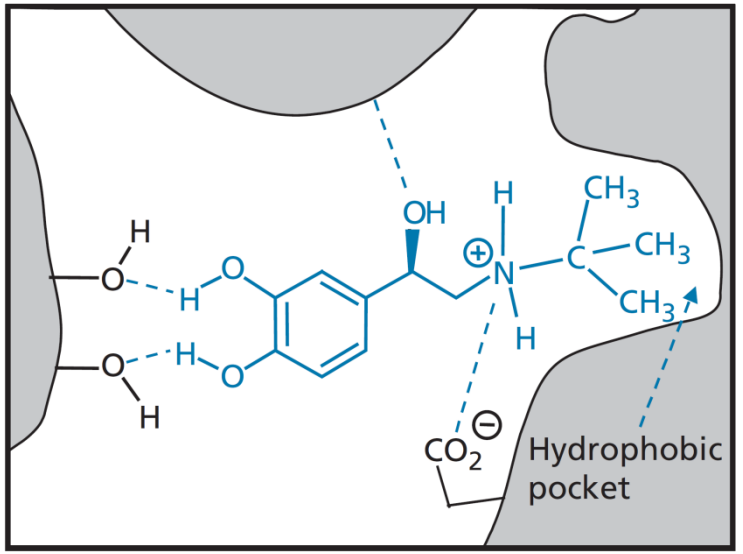
Adrenaline



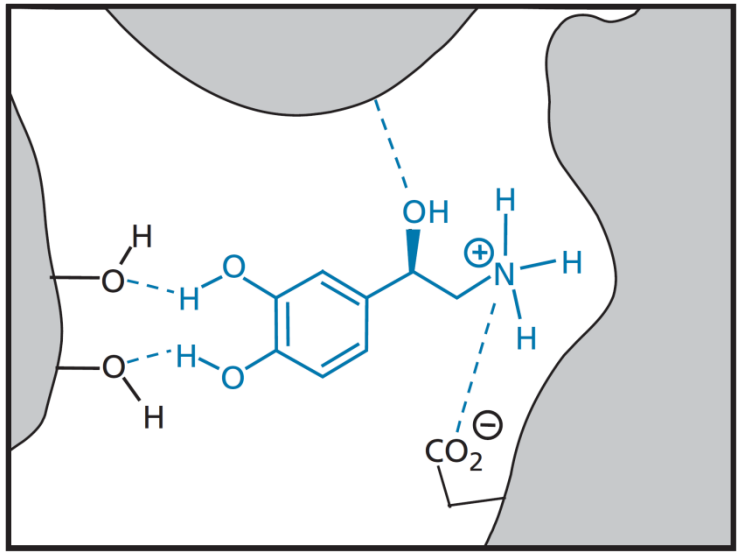
(*R*)-Isoprenaline



2. **Phenol group** is important for α < β
3. **α-Methyl substitution:** $\alpha_2 > \alpha_1$, β



β-Adrenoceptor



α-Adrenoceptor

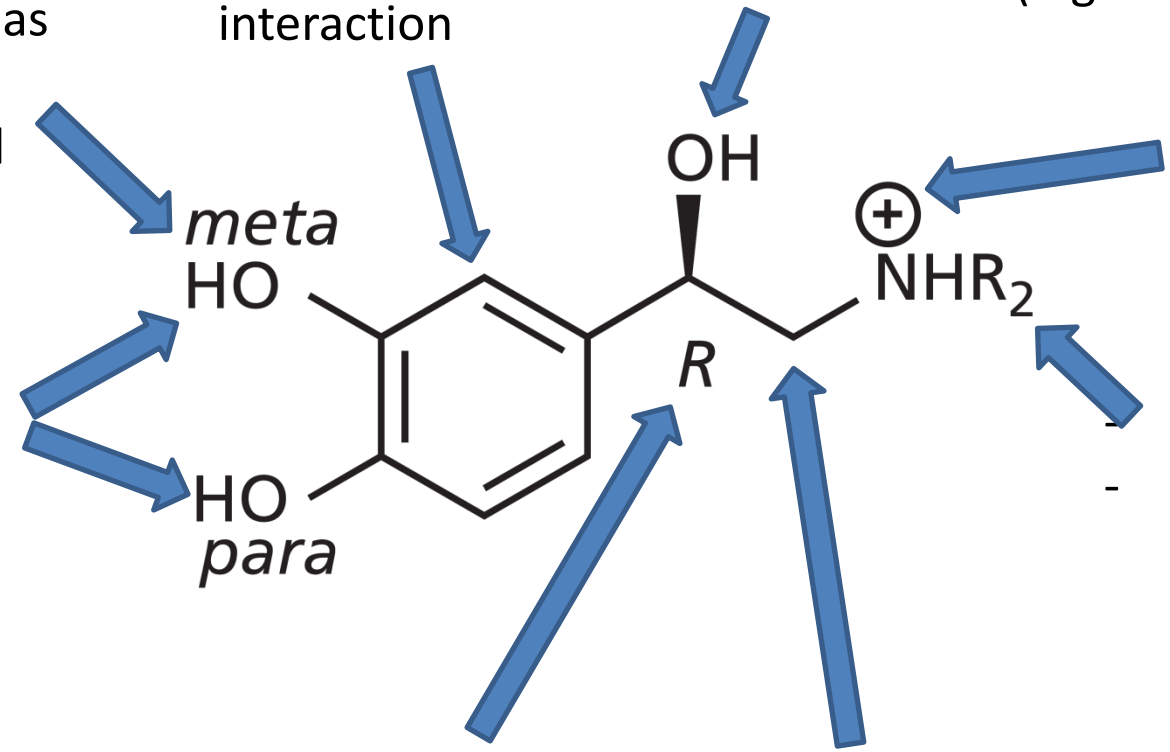
Probably, β-adrenoceptor has a hydrophobic pocket into which a bulky alkyl group can fi t, whereas the α-adrenoceptor has smaller pocket

Only *meta* phenol group, which can be replaced by other H-bond donors such as CH_2OH, CH_2CH_2OH, NH_2 , NHMe, NHCOR, NMe_2, and $NHSO_2R$

- Involved in H-bonds with β-receptors.
- Loss of these groups terminates the activity

Involved in hydrophobic interaction

- Involved in H-bonding
- Removal of OH (e.g. domaine) ➔ ↓activity



Ionized at physiological pH and involved in electrostatic interaction

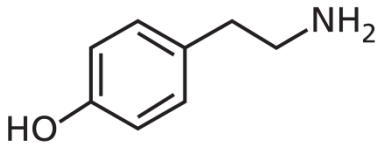
- Activity of 1°, 2° > 3°,4° amines
- Bulky substitution:
  - ↓ affinity to receptors
  - ↑ selectivity for recep. subtypes

R-Enantiomer more active than *S*-enantiomer

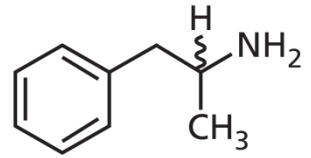
Alkyl substitution ➔

- ↓activity at both α- and β-adrenoceptors
- ↑ selectivity for α_2- adrenoceptors

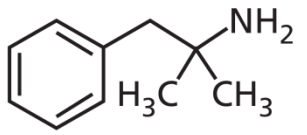
Absence of phenolic OH groups lead to no affinity for adrenoceptors



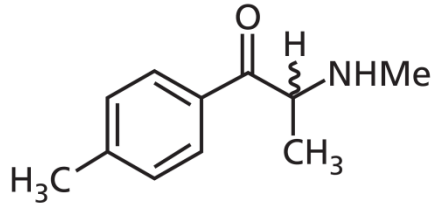
Tyramine



Amphetamine



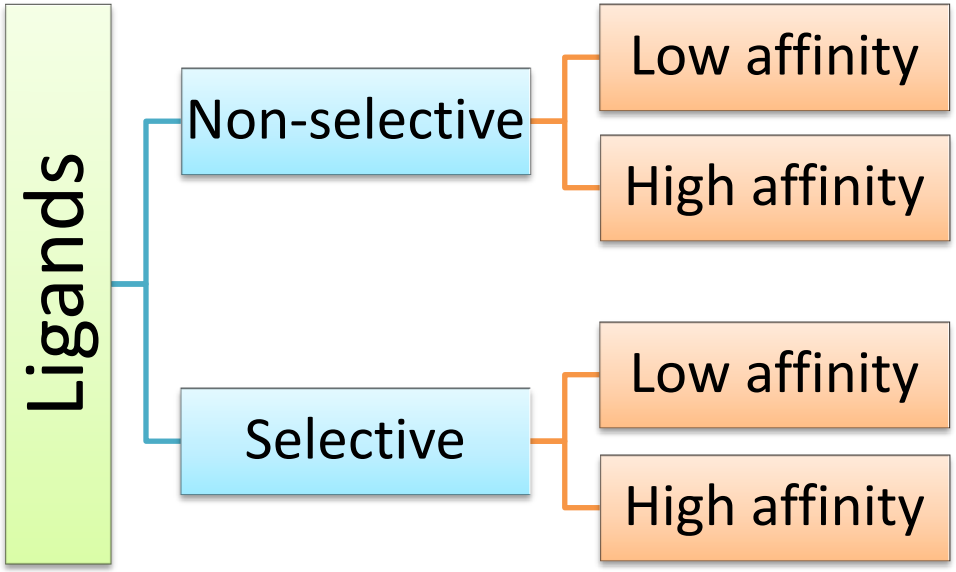
Phentermine



Mephedrone

Selectivity and affinity are different terms

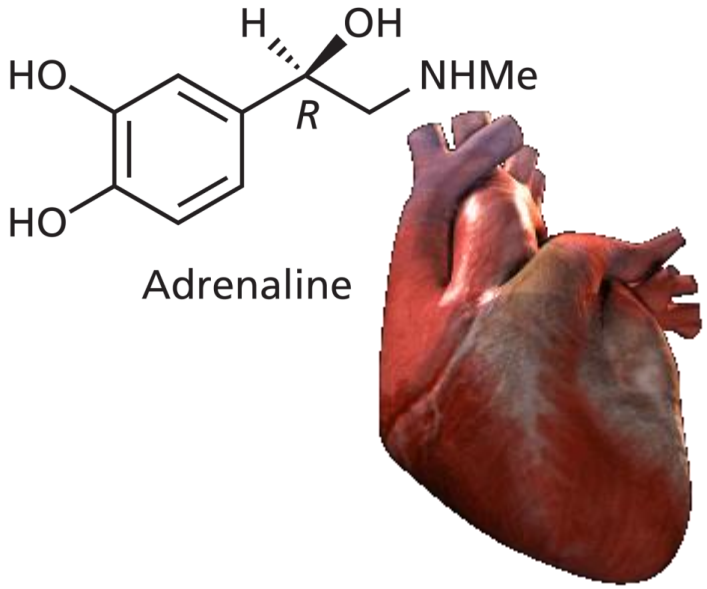
- The combination of selectivity and affinity include



- A non-selective analogue may have higher affinity (to both subtypes) than a selective analogue (to a single subtype)
  Example: Adrenaline (non-selective to α and β) have higher affinity than noradrenaline (selective to α)

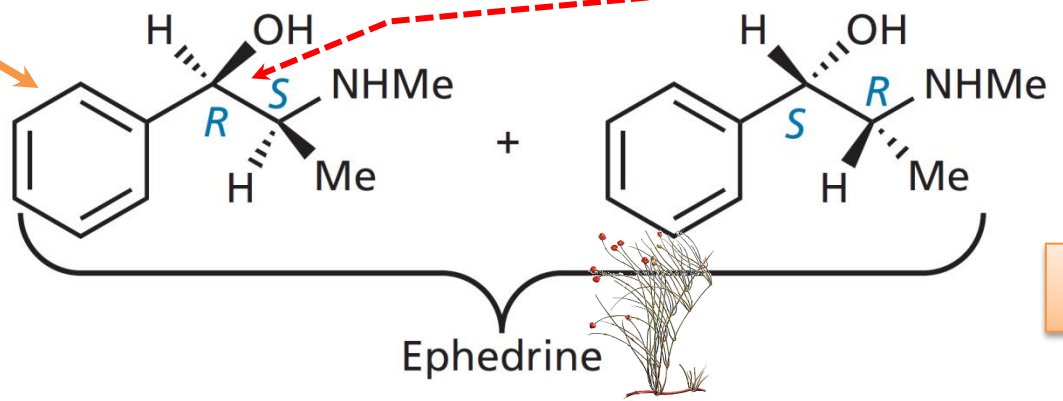
Examples of adrenergic agonists

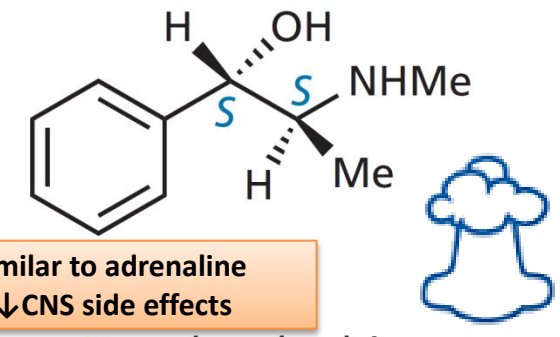
- **Adrenaline** is **non-selective** (activates both α− and β-adrenoceptors), **fast acting** , thus is ideal for emergency **heart stimulant** used in cardiac arrest or anaphylactic shock. But due to its ability to switch ON all adrenoceptors , it has wide range of side effects like: nausea, tachycardia, arrhythmias, hypertension, palpitation, tremor, headache and restlessness.



- **Ephedrine** (from ephedra plant) is available into stereoisomers. It is also **non-selective** (activates both α− and β-adrenoceptors). The absence of phenolic groups lead to **lower affinity to receptors** and **longer half-life** (not metabolized by catechol-O-methyltransferase)), more lipophilic (**cross BBB**) thus used as stimulant.
- **Pseudoephedrine** used as nasal decongestant.

Highest activity since it is stereo-chemically most similar to adrenaline





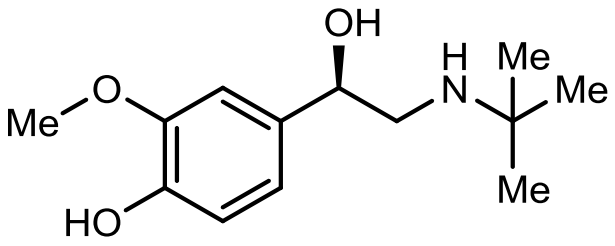
The absence of OH groups lead to:
- Reduce affinity to receptors
- Reduce metabolism ➔↑$t_{0.5}$
- Increase lipophilicity ➔↑ cross BBB
  ➔↑ oral abs.

↓similar to adrenaline
➔↓CNS side effects

α 1 -, α 2 -, β 1 -, and β 3 -Agonists

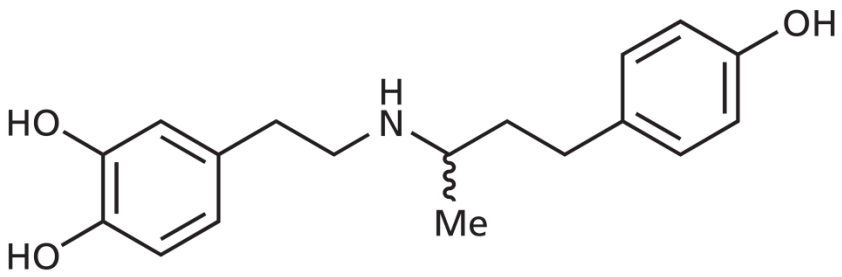
- Agonistic effect against α1 -, α2 -, β1 -, and β3 –adrenoceptors has lower potential for medicinal use, which include:
  - α1-agonist ➔ vasoconstriction: used to localize the effect of dental anesthetic, nasal decongestant
  - α2-agonist ➔ hypotension
  - β1 -agonist ➔ treatment of cardiogenic shock
  - β3 -agonist ➔ anti-obesity

- Agonistic effect against β2 has higher medicinal importance
  - β2 -agonist ➔ bronchodilator



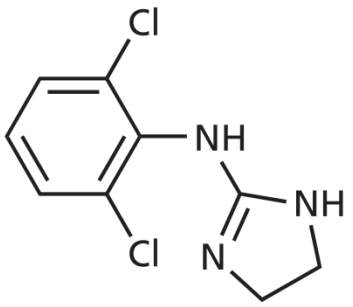
Salbutamol

β2-agonist



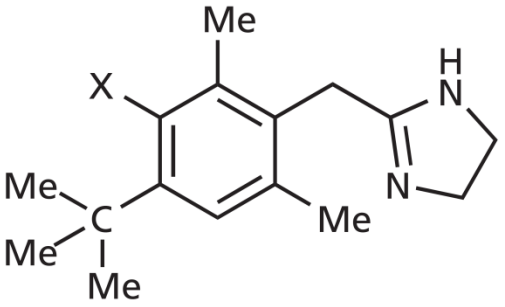
Dobutamine

β1-agonist



Clonidine

α2-agonist



Oxymetazoline; X = OH
Xylometazoline; X = H

α1-agonist

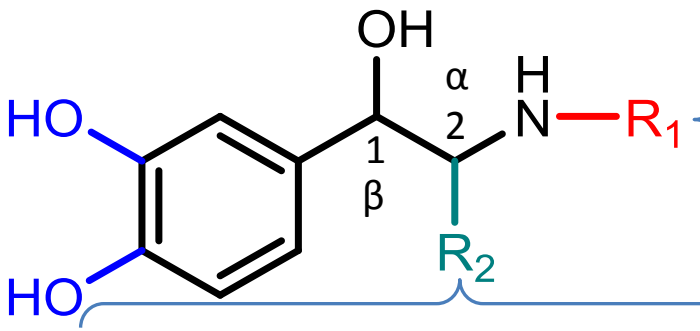
TABLE 16.1 Most Commonly Used Adrenergic Prescription Drugs

Mechanism of Action	Drug	Major Indications
α_1-Agonists	Naphazoline (Privine)	Nasal & ophthalmic congestion
α_2-Agonists	Clonidine (Catapres)*	Hypertension
	Methyldopa (Aldomet)	Hypertension
α_1-Blockers	Prazosin (Minipress)	Hypertension & benign prostatic hyperplasia (BPH)
	Terazosin (Hytrin)*	Hypertension & BPH
	Doxazosin (Cardura)*	Hypertension & BPH
	Tamsulosin (Flomax)	BPH & hypertension
β_2-Agonists	Albuterol (Ventolin)*	Asthma
α_1-, β_1-, & β_2-Blockers	Labetalol (Normodyne)*	Hypertension
	Carvedilol (Coreg)	Hypertension & heart failure
β_1- & β_2-Blockers	Propranolol (Inderal)*	Hypertension, arrhythmias, & angina
	Nadolol (Corgard)*	Hypertension, angina, & hyperthyroidism
	Timolol (Timoptic)*	Glaucoma & hypertension
	Sotalol (Betapace)*	Arrhythmias
	Levobunolol (Betagan)	Glaucoma
β_1-Blockers	Acebutolol (Sectral)	Hypertension, angina, & hyperthyroidism
	Atenolol (Tenormin)*	Hypertension, angina, & hyperthyroidism
	Metoprolol (Lopressor)*	Hypertension
	Bisoprolol (Zebeta)*	Hypertension

*Indicates adrenergic prescription drugs in the top 200 for 2005.

Structural requirements for activity:

1. **β-Phenylethylamine**
2. **Catechol ring**
3. **(1R)-OH**



Aromatic substituents

- **3′,4′-diOH**
  - ➢ α + β activity
  - ➢ ↑ metabolism by COMT➔ ↓ bioavailability and t0.5
  - ➢ Hydrophilic➔↓pass BBB ➔↓ CNS activity
- **3′,5′-diOH** (e.g. metaproterenol)
- **3′-CH_2OH, 4′OH** (e.g. albuterol)
  - ➢ ↑ β2 activity
  - ➢ ↓ metabolism by COMT
- **4′-OH** ➔ ↑ β activity
- **3′-OH** ➔ ↑ α activity (e.g. phenylephrine)
- **No OH** ➔ ↓ α + β activity
  - ➔ indirect activity

R1 substitution

↑ R1 size

- ➢ ↑ β activity
- ➢ (t-butyl ➔ β2)
- ➢ ↓ α activity
- ➢ ↓ metabolism by MAO

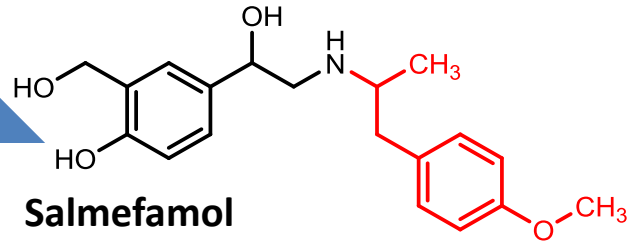
R2 substitution

- ➢ **Small alkyl (Me, Et)**
  - ↓ metabolism by MAO
  - = Metabolism by COMT, = t0.5
- ➢ **Et group**
  - ↑ β activity (e.g. ethylnorepinephrine)
  - ↑ CNS activity .
  - ↑ oral absorption and t0.5
- ➢ **(2S)-methyl** ➔ ↑ α2 activity

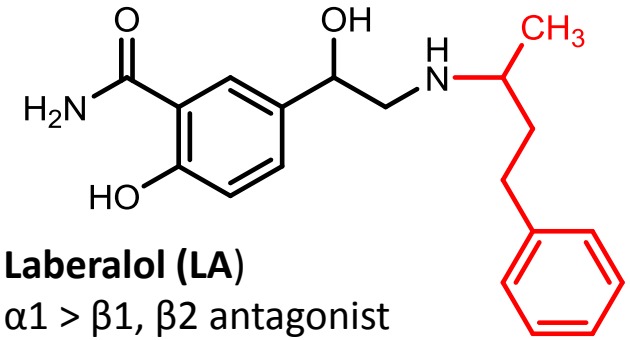
Changes in structure not only affects receptor subtype selectivity, but also affect absorption, oral activity, metabolism, degradation, and thus duration of action

R1 substitution on the amino nitrogen determines α- or β-receptor selectivity.

- As the size of the nitrogen substituent increases, α-receptor agonist activity generally decreases and β-receptor agonist activity increases.
- *N-tert*-butyl group enhances β2-selectivity. For example, *N-tert*-butylnorepinephrine (Colterol) is 9 to 10 times more potent as an agonist at tracheal β2-receptors than at cardiac β1-receptors.
- **Larger than butyl group changes the activity to antagonism (specially α1-blocking activity) and reduce metabolism by MAO (e.g. tamsulosin and labetalol); unless terminated by polar group (e.g. salmefamol)**

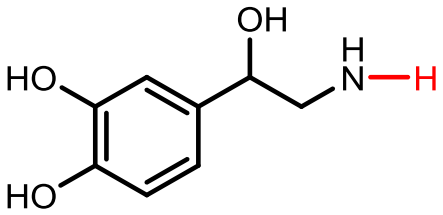


Salmefamol
β1 < β2 agonist
(Potent selective β2 agonist)

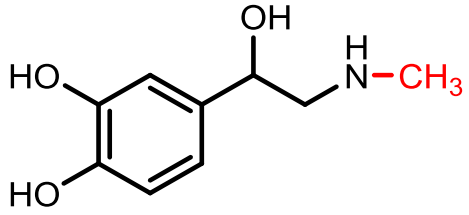


Laberalol (LA)
α1 > β1, β2 antagonist
(Non-selective α1 **antagonist**)

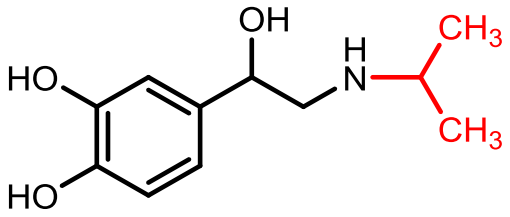
Increase bulkiness of R1



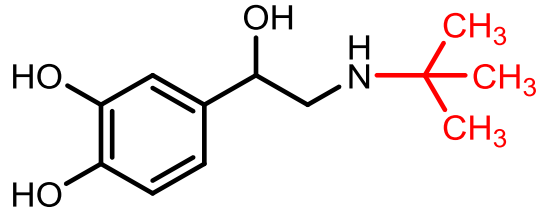
Norepinephrine (NE)
α > β agonist
(Selective α agonist)



Epinephrine (E)
α, β1 and β2 agonist
(Non-selective α, β agonist)

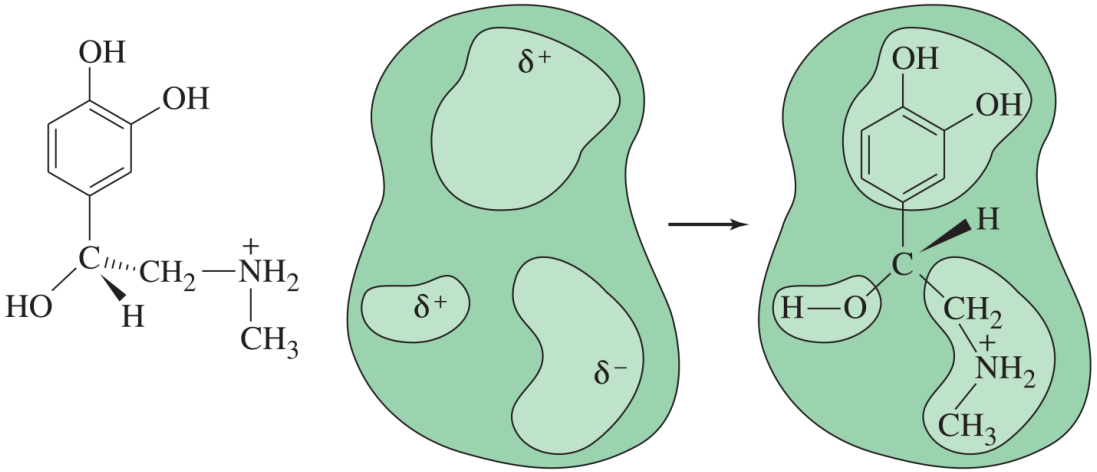


Isoproterenol (ISO)
β1 and β2 agonist
(Non-selective β agonist)

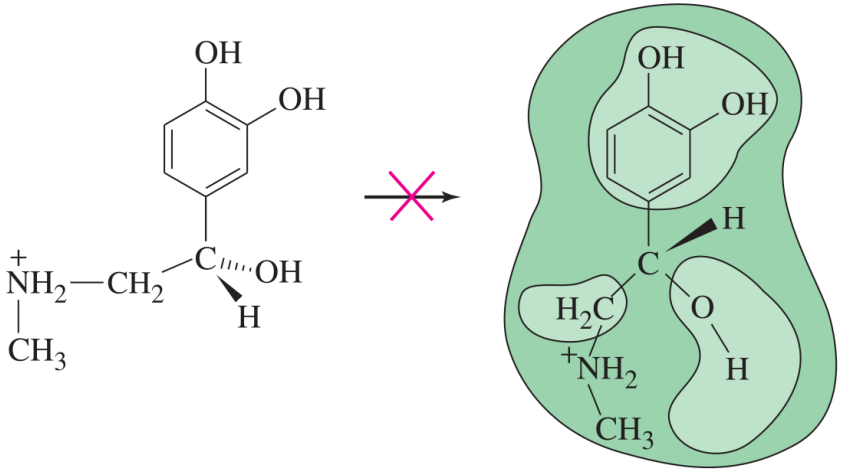


N-t-Butylnorepinephrine (Colterol)
β2 agonist
(Selective β2 agonist)

- Stereochemistry for CAs analogues is important for activty.
- Substitution on either carbon-1 or carbon-2 yields optical isomers. (1*R*,2*S*) isomers seem correct configuration for direct-acting activity.
- 1*R* configuration of adrenaline binds receptor by 100-fold higher than 1*S* configuration.



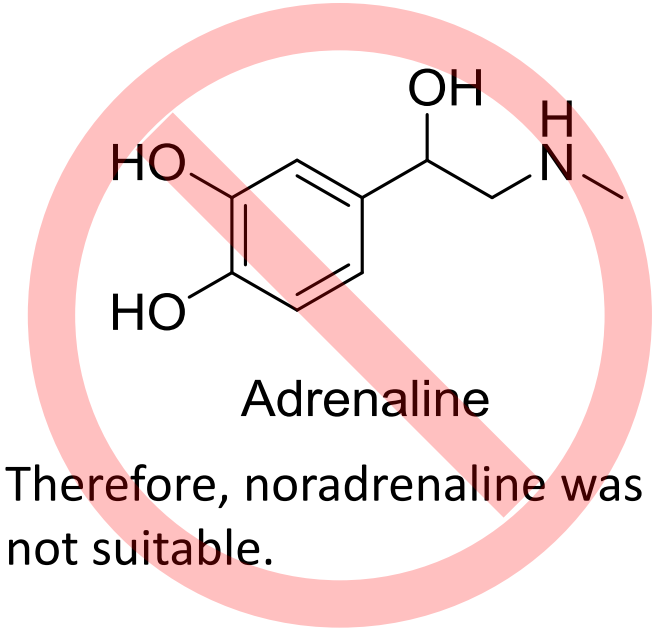
(*R*)-(−)-epinephrine
natural epinephrine



(*S*)-(+)-epinephrine
unnatural epinephrine

Case study: Development of anti-asthmatic drugs

- Most β2-agonists are used as bronchodilators for asthma and other constrictive pulmonary conditions. They are also used to relax smooth muscles of uterus.
- The bronchodilators should be:
  1. Selective β2-agonists are required to avoid stimulating β1-receptors and α-receptors
  2. Have long duration of action (lipophilic and slowly metabolized by MAO and COMT)

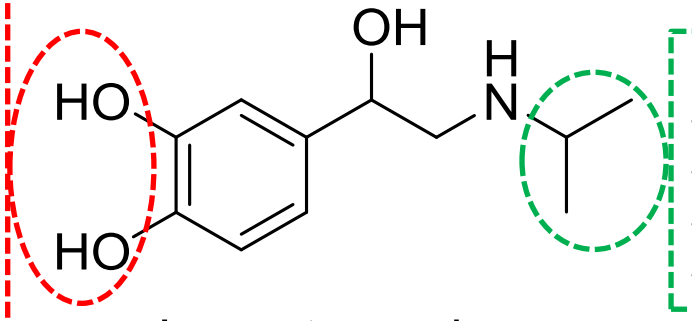


Adrenaline

Therefore, noradrenaline was not suitable.

- Isoproterenol was the lead compound used. It is selective β-agonist, thus stimulate both β1- and β2-receptors. **It also increases heart rate**.

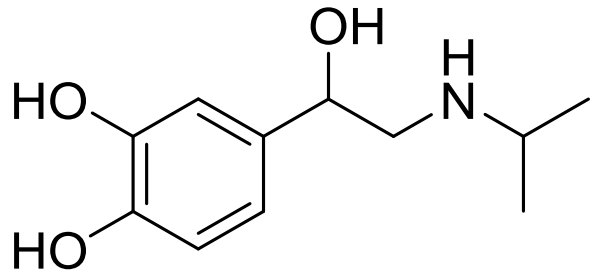
Di-hyroxyl groups:
- Sensitive to air and light
- Metabolized by
  - COMT
  - Sulfate conjugation
  - Glucuronide conjugation
- **Low oral bioavailability**
- **Short duration of action**



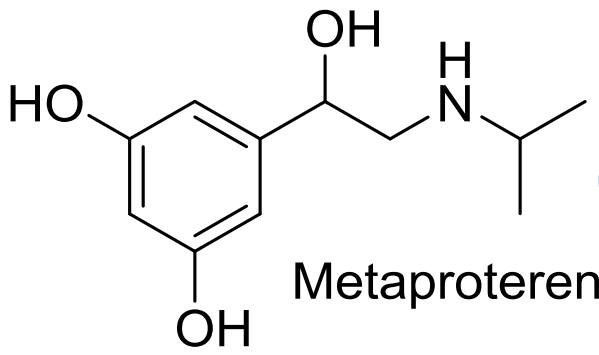
Isoproterenol

Isopropyl group:
- ↑β activity
- ↓α activity
- ↓ metabolism by MAO
- **Long duration of signal**

Case study: Development of anti-asthmatic drugs (Cont.)

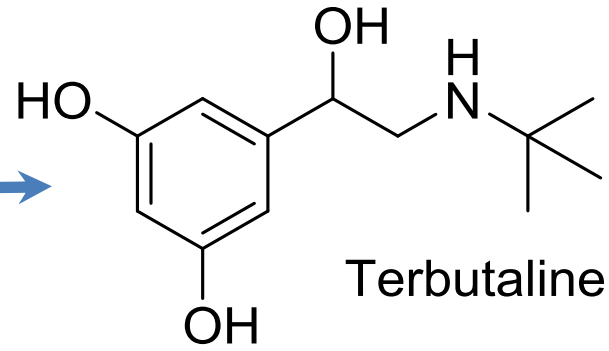


Isoproterenol



Metaproterenol

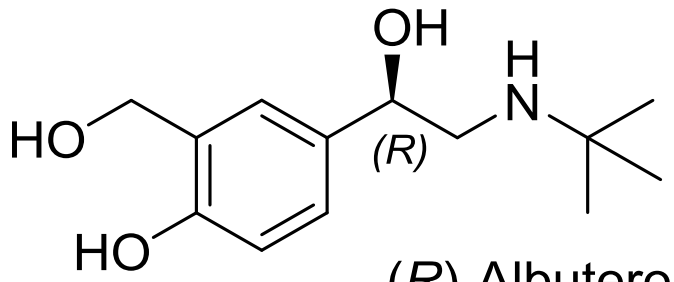
Has resorcinol group, thus more **β2 selective, not** metabolized by COMT, and more **orally bioavailable**



Terbutaline

Has bulky N-R group, thus even more **β2 selective** and **resist** metabolism by MAO, more **orally bioavailable** and **have long duration of action and signal**

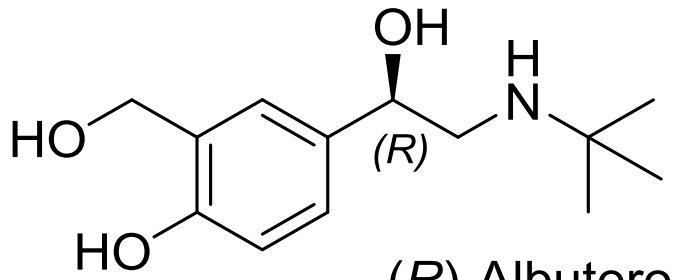
But has LOWER AFFINITY to receptor



(*R*)-Albuterol
or (*R*)- salbutamol

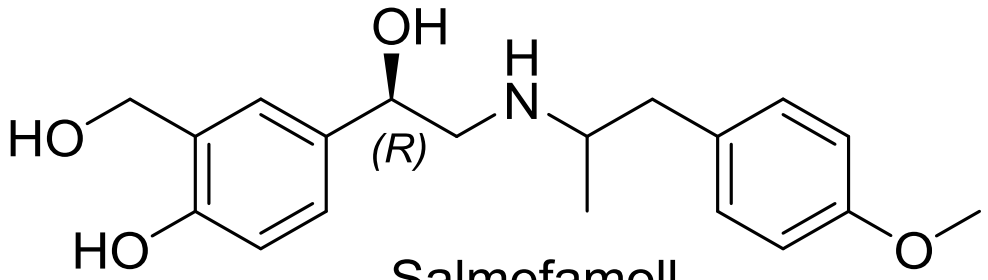
Has methylene hydroxyl subst.
(R)-isomer is agonist (used)
(S)-isomer is antagonist (not used)

Case study: Development of anti-asthmatic drugs (Cont.)



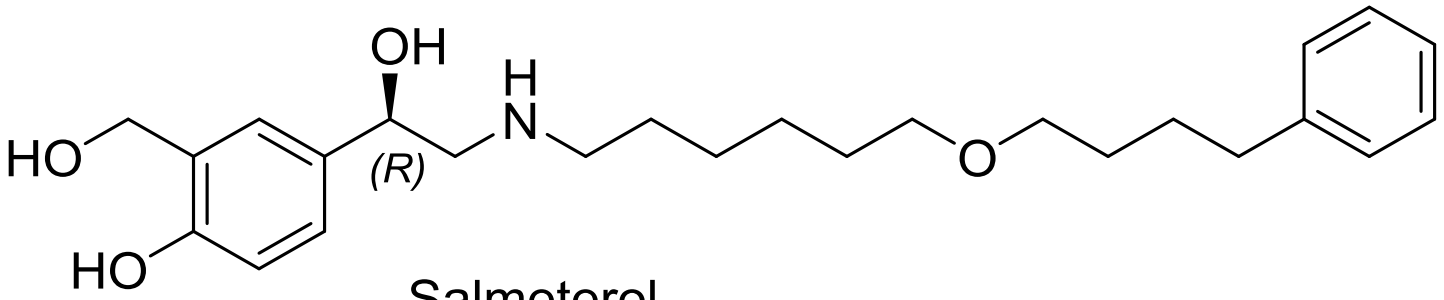
(*R*)-Albuterol
or (*R*)- salbutamol

2000 times less active on the heart.
a duration of action of 4 hours.
Is not metabolized by COMT.
R enantiomer is 68 times more active than *S*.
The pure *R* isomer has been prepared and marketed (levalbuterol)….. This is what is called chiral switching.



Salmefamoll

1.5 times more active than salbutamol
Longer duration of action (6hr)

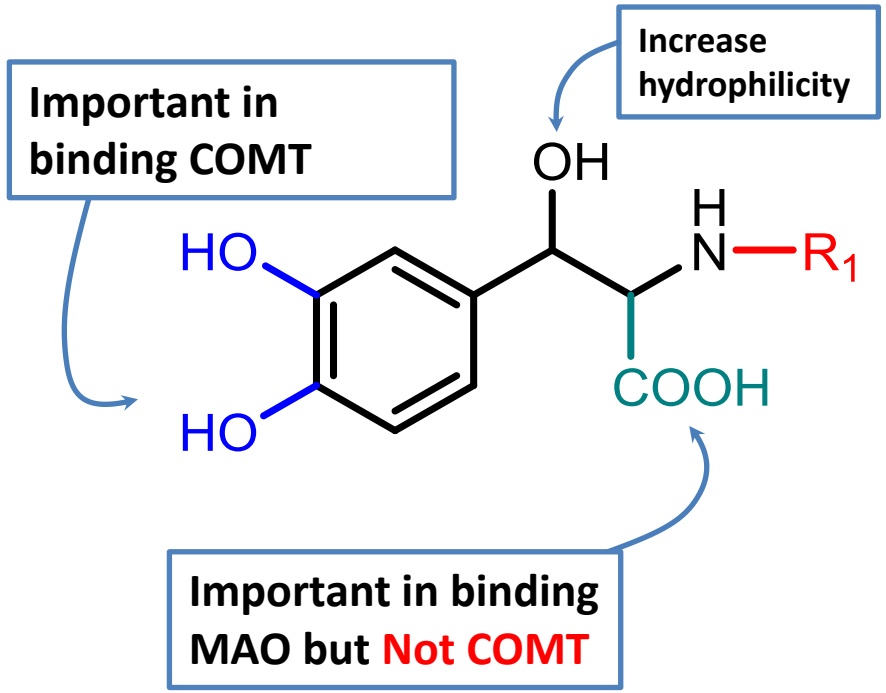


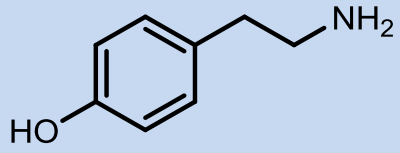
Salmeterol

2 times more active than salbutamol
Longer duration of action (12hr)

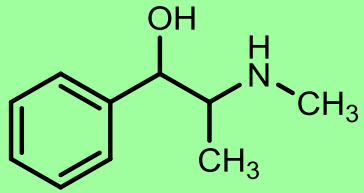
R2 substitution on the alpha carbon and the indirect acting phenylethylamines.

- The indirect-acting phenylehtylamines (non-CAs) contains **NO phenyl-dihydroxyls**, thus not bind to adrenergic (GPCR switch) and not deactivated by COMT. Only releases **neuronal** vesicles
- should be resistance to MAO in order to be effective, therefore all of them have no α-COOH group.
- Some non-CAs contain Cβ-OH ➔↑binding to switch (if *R*), ↑polarity
- Some non-CAs contain Cα-CH_3 which
  - Increases lipophilicity (which increases oral absorption, t0.5 and penetration of BBB)
  - Increases resistance to MAO.
  - Decreases binding to GPCR switch (to α1 more than β)

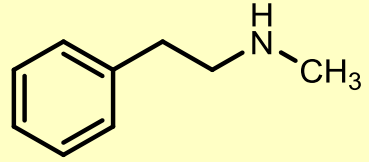




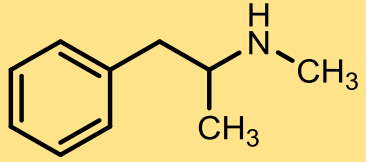
***P*-Tyramine (Log P =0.97)**
Activity at α, β **neurons**



Ephedrine (Log P =1.05)
Activity at α, β **neurons**
(mainly used for peripheral effects)



Amphetamine (Log P =1.8)
Low Activity at α, β **neurons**
(mainly used for CNS effects)

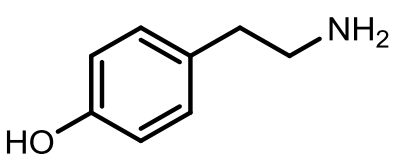


Methamphetamine (Log P =1.97)
Low activity at α, β **neurons**

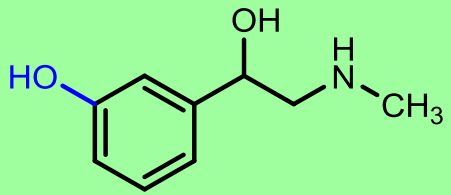
Increase lipophilicity and increase in CNS effect

Aromatic hydroxyls

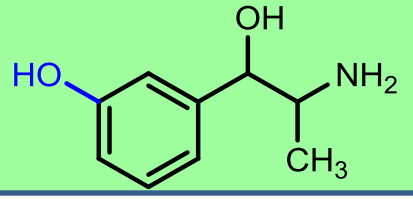
- Maximum binding to α and β adrenergic switches depends on 3′-OH and 4′-OH.
- 3′-OH only reduces affinity to both α and β, but it is more reduced for β, thus ➔ α-selective.
- receptors but mainly and preserve it forNo 4′-OH lead to no binding to β2 unless 5′-OH is present.
- It appears that the catechol moiety is more important for α2-activity than for α1-activity especially *p*-OH (4′) group.
- **The presence of 3′-OH only, eliminates binding to β switches and preserve it for α switches**



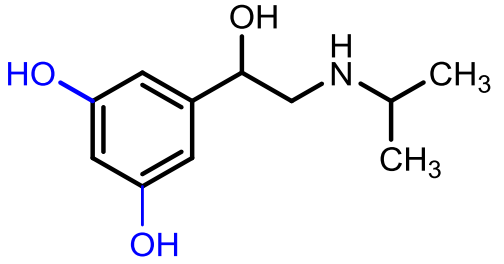
***P*-Tyramine (Log P =0.97)**
No activity at α, β switches



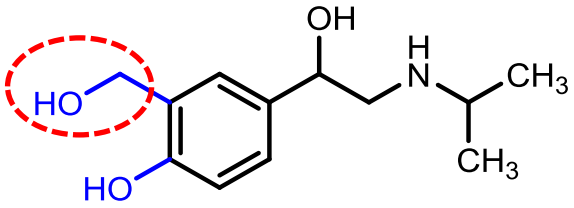
Phenylephrine (Log P= 0.68)
Lower activity at α, β than NE
(Almost selective α1 agonist)



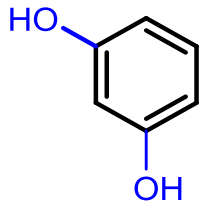
Metaraminol (Log P= 0.68)
Lower activity at α, β than NE
(Almost selective α1 agonist)



Metaproterenol (Log P= 0.28)
Resist COMT➔ ??
(Selective β2 agonist)



Albuterol (Log P= 0.75)
Resist COMT➔ ??
Better oral absorption
(Selective β2 agonist)

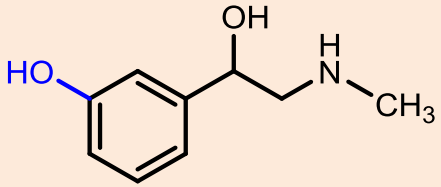


Resorcinol: can be used to design selective β2 agonist agonists
Resist COMT➔ lower metabolism ➔ ↑$t_{0.5}$

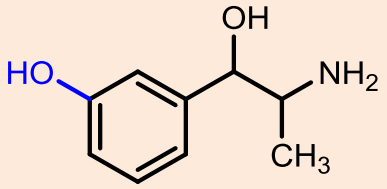
Selective α1-agonists

1. Phenylethanolamines

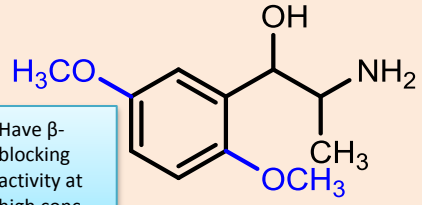
Usually have *meta*-OH and **NO** *para*-OH groups at the phenyl



Phenylephrine



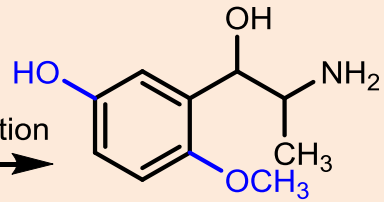
Metaraminol



Have β-blocking activity at high conc.

Methoxamine (inactive)

5'-O-demethylation



(active)

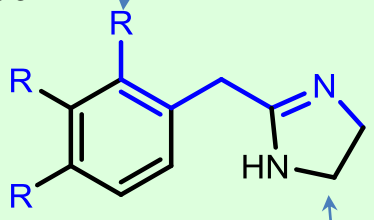
Pharmacologically

1. Strong vasoconstrictors
2. Have minimum cardiac stimulation
3. Long $t_{0.5}$ (**NOT** good substrates for COMT)
4. Used for hypotension and as nasal decongestant

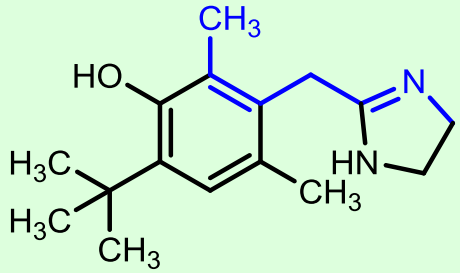
2. Arylimidazolines

Contain a one atom bridge between C2 of the imidazoline ring and a phenyl substituent. The overall structure is similar to phenylethanolamine

Important for agonistic effect on α1 and α2

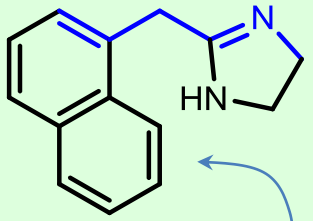


Destroy agonistic effect on α2
(thus they are absent in α2-agonists)



Oxymetazoline

Imidazoline moiety (Pka= 9-10) is mostly ionized at blood pH ➔ low CNS side effects



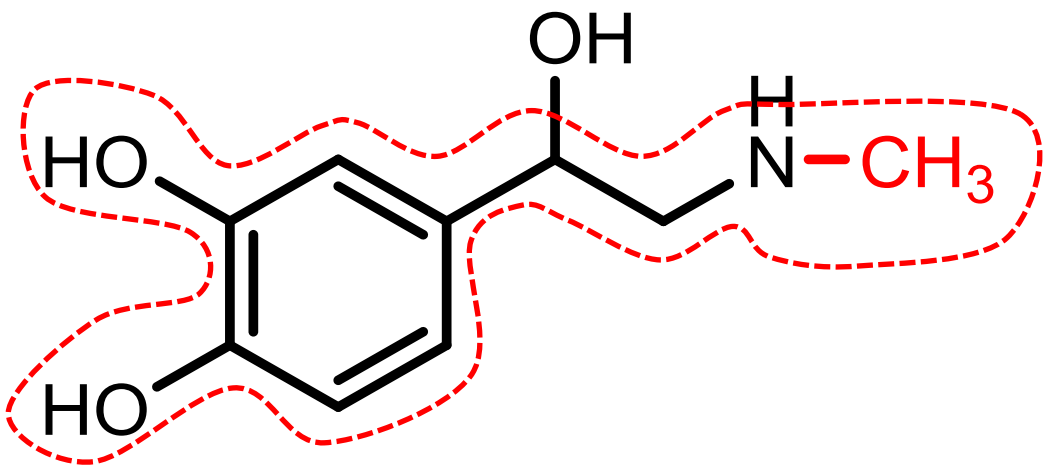
Naphazoline

Phenyl rings are *ortho* fused

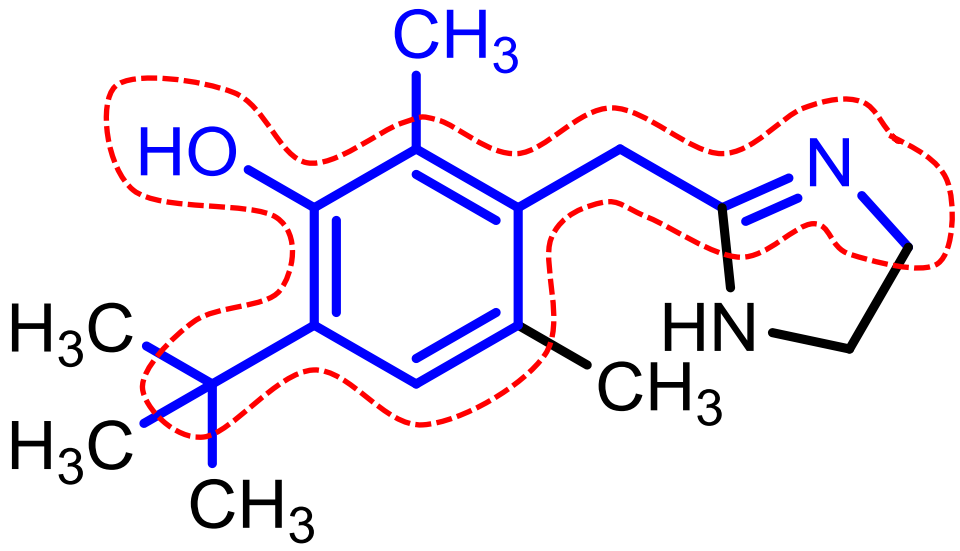
Pharmacologically

1. Strong vasoconstrictors
2. Used as nasal decongestants and as eye drops

Selective α1-agonists (Cont.)



Phenylethanolamines



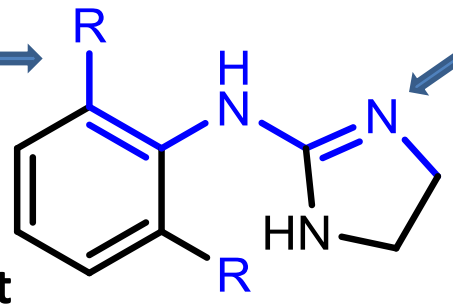
Oxymetazoline

Selective α2-agonists

- **They are closely related structurally to the imidazoline nasal decongestants, however acting more on α2-receptors in brain:**

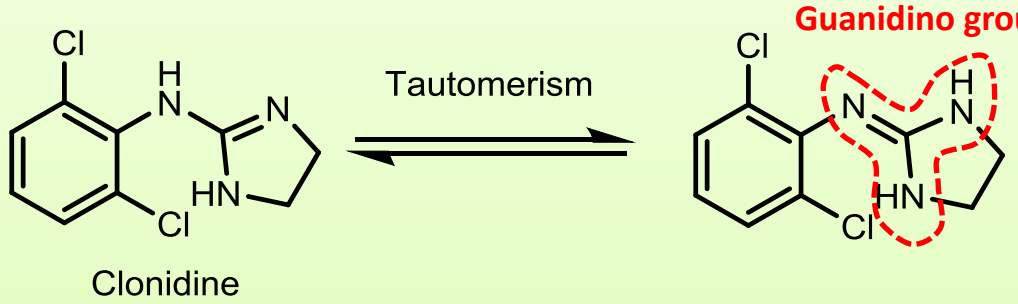
1) With bulky lipophilic group at *ortho*-positions of phenyl.
↑ Lipophil. ➔ ↑ cross BBB

2) With no bulky lipophilic group at *meta*- or *para*- positions of phenyl.



3) Have N as linker between imidazoline ring and phenyl ➔ tautomerism

The tautomerism ➔ ↓ pKa ➔ ↓ ionization in blood pH ➔ ↑ penetration to CNS ➔ bind α2-receptors in brain ➔ 1. lower blood pressure and 2. cause sedation



Clonidine

- The *ortho*-substituents➔↓flexibility ➔↑selectivity
- p*K*a of 8.3 and is approximately 80% ionized at physiologic pH
- positive charge is shared through resonance by all three nitrogens of the guanidino group ➔ ↓ pKa

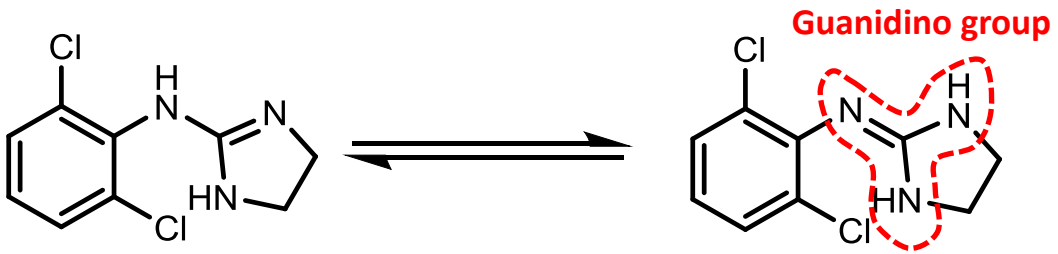
Pharmacologically

1. Vasoconstriction followed by vasodilatation
2. Used for hypertension
3. Long $t_{0.5}$ (**NOT** good substrates for COMT)
4. Due to binding to α2-receptors in brain, they can also be used for glaucoma, spasticity, migraine prophylaxis, opiate withdrawal syndrome, and anesthesia.

Selective α2-agonists

- Three subtypes of a2-adrenoceptors, α2A (brain area controls CVS), α2B (vascular postdynaptic), and α 2C (brain area controls pain and spasm) ,:

- Lower flexibility lead to selective agonistic effect on alpha receptors
- Selective antagonistic effect on beta receptors



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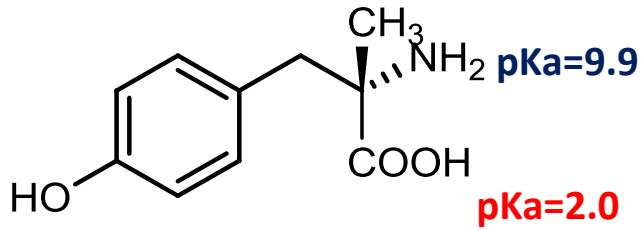
Indirect-acting sympatholytics

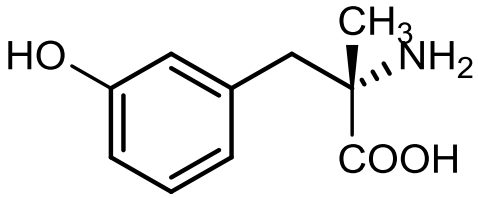
1. Tyrosine hydroxylase inhibitors:

- The compounds inhibit tyrosine hydroxylase (the first enzyme in CAs biosynthesis).
- They are L-tyrosine analogues having α-methyl substitution.
- **Metyrosine** inhibit TH and lead to formation of false neurotransmitters.
- The stereochemistry of alpha carbon should be preserved as in L-tyrosine.
- It is used orally for few days as preoperative management of pheochromocytoma (adrenal medulla tumors)
- Similar compound is α-methyl-*m*-tyrosine which have *m*-hydroxyl instead of normal *para*-hydroxyl



α-methyl tyrosine (**Metyrosine**)

- Amphoteric ➔ ↓ solubility in urine ➔ crystal urea
- Log P=0.73,
- Used to reduce blood pressure

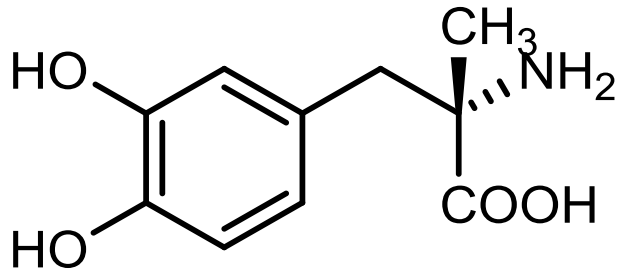


α-methyl-*m*-tyrosine

Indirect-acting sympatholytics

2. L-amino acid decarboxylase inhibitors:

- The compounds inhibit dopa decarboxylase (the second enzyme in CAs biosynthesis).
- They are L-tyrosine analogues having α-methyl substitution.
- Carbidopa has proven clinically useful, but not as modulators of peripheral adrenergic transmission.
- It used instead in combination with L-Dopa in treatment of parkinsonism in order to reduce the peripheral production of CAs in response to the intake of L-Dopa
- Carbidopa is very similar to metyrosine, however having *meta* and *para*- dihdyroxyl groups

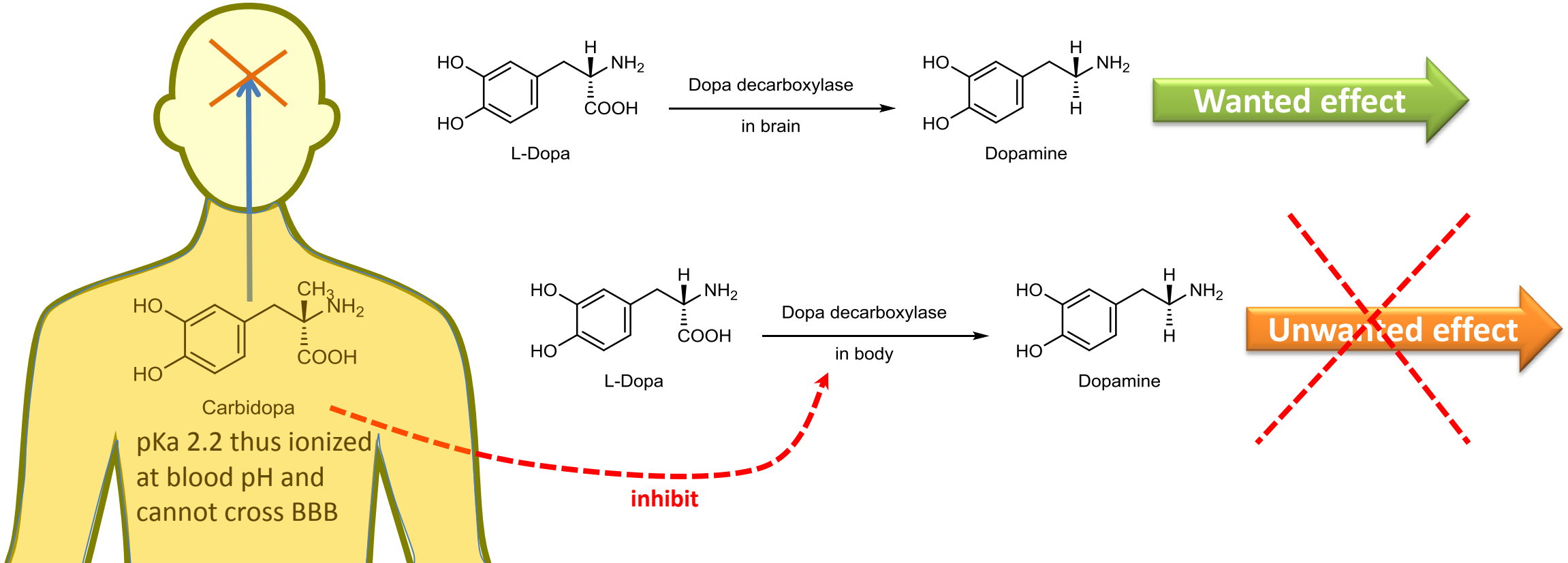


Carbidopa

- pKa 2.2 thus ionized at blood pH and cannot cross BBB

Indirect-acting sympatholytics

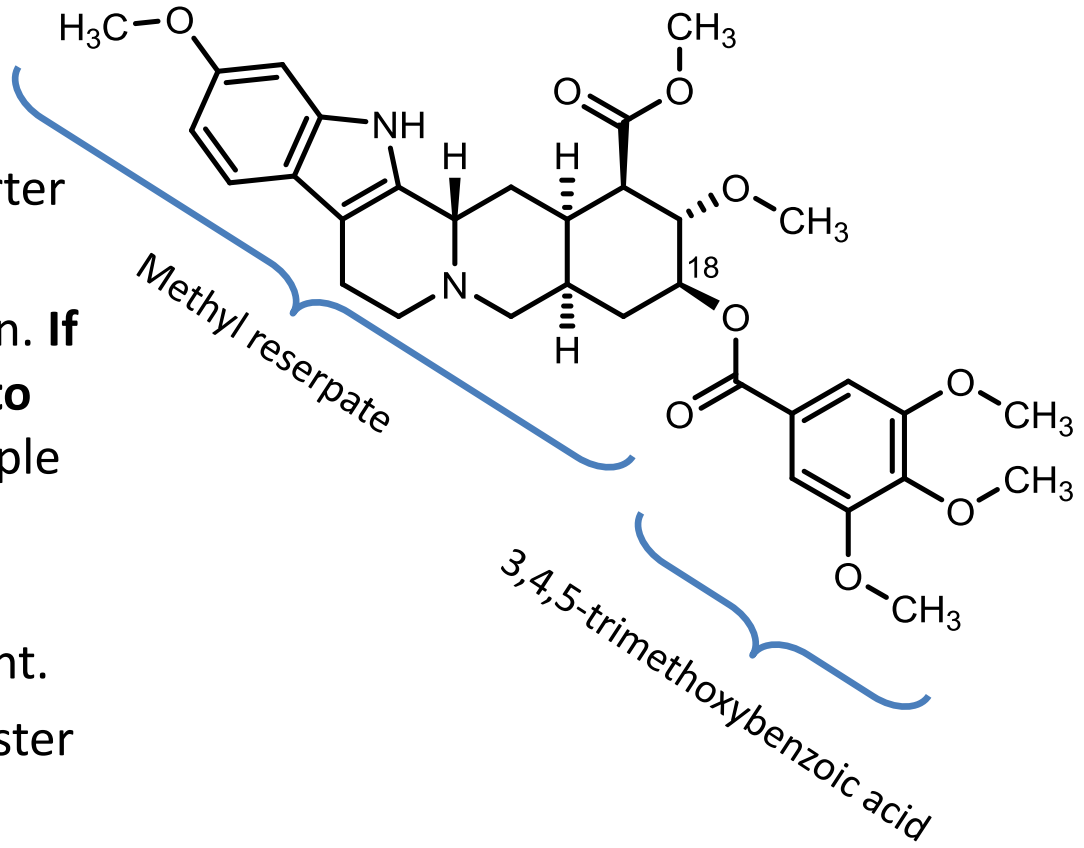
- Dopa decarboxylase
  - Is present in brain and other tissues
  - Can decarboxylate L-tyrosine as well as L-tryptophane and L-phenylalanine
- L-Dopa used as precursor for dopamine to treat parkinsonism, however it is combined with carbidopa (an ionized decarboxylase inhibitor) to reduce the side effects



Indirect-acting sympatholytics

3. CAs packaging inhibitors:

- The compounds inhibit the vesicle monoamino transporter (VMAT) which transport CAs into vesicles.
- It inhibit the packaging of NE as well as DA and serotonin. **If not packed, the CAs will be metabolized by MAO lead to depletion**. Thus the pharmacological effect delayed couple of weeks from use startup or stop.
- Reserpine is an indole akaloid obtaind from the root of *Rauwolfia serpentina.* It is used as antihypertensive agent.
- It is extensively metabolized through hydrolysis of the ester function at position 18 and yields methyl reserpate and 3,4,5-trimethoxybenzoic acid.
- It decomposed by light and oxidation. NE second enzyme in CAs biosynthesis.



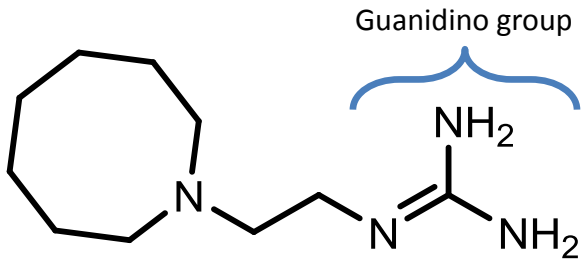
Reserpine

- Cross BBB (Log P =4.4)
- CNS side effects such as psychotic **depression**
- , Log D = 3.9

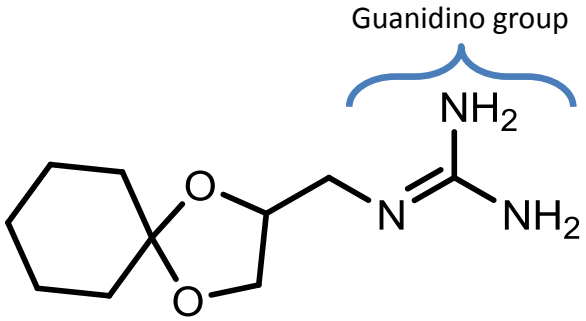
Indirect-acting sympatholytics

4. CAs vesicle stabilizer:

- The compounds stabilize the CAs vesicles membrane and inhibit their exocytosis.
- The compounds have guanidino moiety attached to either hexahydroazocinyl ring (guanethidine) or dioxaspirodecyl ring (guanadrel).
- They have highly basic amines (pKa >13) that are completely protonated at physiological pH ➔ ↓cross of BBB ➔ ↓CNS side effects.
- The oral absorption for guanethidine < guanadrel, probably through active transport.



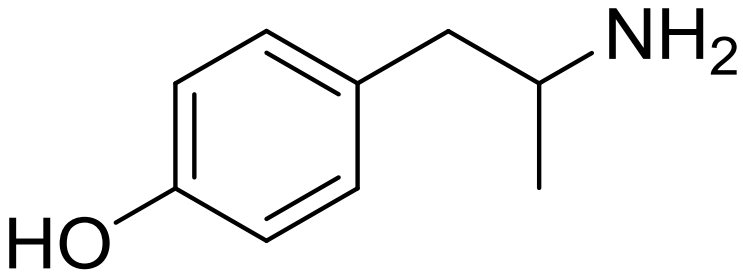
Guanethidine
(Log P =0.77)



Guanadrel
Log P =0.57

Case study: indirect acting adrenergics

- **Hydroxyamphetamine**
- Is similar to amphetamine but more hydrophilic ➔ ↓ cross BBB ➔ ↓ CNS stimulation
- Used to dilate pupil during eye examination and surgery



Hydroxyamphetamine
Log P= 1.07
pKa= 10.71